

World Federation of Neurology

Seminars in  
Clinical Neurology

# Neurologic Consequences of Malnutrition

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**FACULTY**

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## NEUROLOGIC CONSEQUENCES OF MALNUTRITION

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NEUROLOGIC CONSEQUENCES OF MALNUTRITION

Marco T. Medina, MD, Chair

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## Neurologic Consequences of Malnutrition

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# Preface

The recent report from the World Health Organization (WHO), *Neurological Disorders: Public Health Challenges*, reveals that up to one billion people worldwide are affected by neurologic disorders, constituting 6.3% of the global burden of diseases. This is a strong warning about the overall impact of these disorders, which are also an important cause of mortality and already represent 12% of total deaths around the world. In addition, 92 million of daily-adjusted life years (DALYs) were lost in 2005 as a direct result of this group of diseases and a rising trend is being projected. Neurologic disorders affect people in all countries, irrespective of age, sex, education, or income.

Disorders related to malnutrition, while potentially preventable, produce moderate to severe disabilities. Nearly 800 million people in the world do not have enough to eat, most of them living in developing countries. In these regions, inadequate amounts of food (causing conditions such as child malnutrition and retarded growth) and inadequate diversity of food (causing micronutrient deficiencies) continue to be priority health problems. Malnutrition increases the risk of disease and early death and affects all age groups, but it is especially common among poor people and those with inadequate access to health education, clean water, and sanitation.

Continuing with the *Seminars in Clinical Neurology* series, the World Federation of Neurology (WFN) would like to emphasize (1) the significance of neurologic diseases related to malnutrition, (2) the importance of early detection and opportune treatment, particularly to avoid development abnormalities, and (3) the severe physical disability that they can produce. Since this material is directed to neurologists from underdeveloped countries, this text has been divided into topics that we consider to be useful for specialists who have a lack of resources and are exposed to a significant number of patients with these types of disorders. As chair of this course, we (1) assembled a multinational group of expert neurologists who remain in permanent contact with patients that suffer neurologic diseases associated with malnutrition, (2) performed an extensive review of recognized literature, particularly from developing countries, and (3) added interesting clinical cases that we considered to be educationally beneficial for the reader.

In Chapter 1, Drs. Rodríguez-Salinas, Amador, and Medina provide a global overview of the epidemiology and magnitude of malnutrition and neurologic disorders. A brief explanation of the clinical and functional assessment of undernourished patients is described, particularly in patients with serious protein-energy malnutrition (PEM) which can lead to severe clinical presentations of *marasmus* and *kwashiorkor*. Finally, an extensive and complete classification of the different micronutrient deficiencies related to neurologic syndromes is presented along with a complete description of each of these entities and the secondary disorders that they produce.

Dr. Holden shows us that nutrients clearly play a direct role in the neurobiology of the central nervous system and consequently in its development (Chapter 2). The severity of the impact of malnutrition depends on the severity and duration of the nutritional deficiency, the

developmental stage at which the deficit occurred, the preexisting biological condition of the child, and the socio-economic context of the child. Factors such as the amount of breast feeding, a small for gestational age birth weight, and deficiencies in iodine, iron, or protein can be associated with long-term deficits in cognition, school achievement, and behavior. An encouraging note is the degree to which the neurologic system can recover from the impact of malnutrition under certain conditions.

In Chapter 3, Dr. Ana Morales-Ortíz, with the assistance of Dr. Rodríguez-Salinas and Dr. Medina, establishes the relationship between alcoholism and malnutrition. This association is a major public health challenge in developing nations. Globally, the incidence of malnutrition in chronic alcoholics is estimated to be between 5 and 40%. Alcohol can produce malnutrition through two mechanisms: a primary mechanism which replaces other nutrients in the diet and a secondary mechanism which produces a reduction in absorption, digestion, and use of essential nutrients. A considerable number of neurologic diseases are the result of this harmful association.

Finally, Dr. Hernández-Toranzo et al in Chapter 4, describe the different neurophysiologic findings in undernourished patients.

We present this material in an effort to provide a useful source for neurologists in developing countries as they confront neurologic diseases related to malnutrition.

Marco T. Medina, MD  
Tegucigalpa, Honduras

# Editor's Preface

The mission of the World Federation of Neurology (WFN) is to develop international programs for the improvement of neurologic health, with an emphasis on developing countries. A major strategic aim is to create and promote affordable and effective continuing medical education materials specifically for neurologists and related health care providers. The *WFN Seminars in Neurology*, initiated by its first editor-in-chief, Theodore L. Munsat, MD, uses an instructional format that has proven to be successful in controlled trials of educational techniques. Modeled after the American Academy of Neurology's highly successful *Continuum*, we use proven pedagogical approaches to enhance the effectiveness of each course. These include case-oriented information, key points, multiple-choice questions, annotated references, and abundant use of tables and illustrations.

The WFN has recognized the unmet needs of neurologists who must practice medicine without many of the advantages that are often taken for granted in the industrialized world. This text is one in a series of courses designed to address issues related to the practice of neurology in regions with limited resources, tropical conditions, and sociocultural traditions that are unique to developing areas of the world, and which are not covered in standard textbooks. The most important investment in health care delivery in these regions, however, is in properly trained medical personnel, and neurologic specialists who play an essential role not only as caregivers, but as educators. With this in mind, we have asked course faculty to present the instructional material and patient care guidelines with minimal reference to expensive or unproven diagnostic and therapeutic approaches, without compromising the goal of achieving the very best available care for patients with neurologic disorders. When necessary, a choice of approaches is presented to account for different levels of available resources.

*Neurologic Consequences of Malnutrition*, edited by Marco Medina, MD, addresses a crucial cause of neurologic dysfunction that is particularly prominent in the developing world. It is available free of charge on the WFN website ([wfneurology.org](http://wfneurology.org)), and hard copies can be purchased at a nominal fee from the publisher. This is an unusual distribution process for continuing education material, designed for universal availability. Limited numbers of hard copy courses can also be made available without charge to qualifying membership societies, with the condition that they be used to convene discussion groups, which are an important component of the learning experience. Funding for this program is provided by unrestricted educational grants.

Jerome Engel, Jr., MD, PhD  
Los Angeles, California



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World Federation of Neurology  
Seminars in Clinical Neurology

## NEUROLOGIC CONSEQUENCES OF MALNUTRITION



# MALNUTRITION AND NEUROLOGIC DISORDERS: A GLOBAL OVERVIEW

Luis C. Rodríguez-Salinas, Claudia Amador, and Marco T. Medina

Suitable nutrition is the basis to assure a healthy life and the normal development of an individual. Proper nutrition means that children develop stronger immunological systems, with fewer diseases and with better possibilities of learning. It implies a more productive people, which can help create opportunities to gradually break the cycles of both poverty and hunger in a sustainable way. Freedom from hunger and malnutrition is a basic human right, and their presence is unacceptable in a world that has both the knowledge and the resources to end this human catastrophe (World Declaration on Nutrition, 1992).

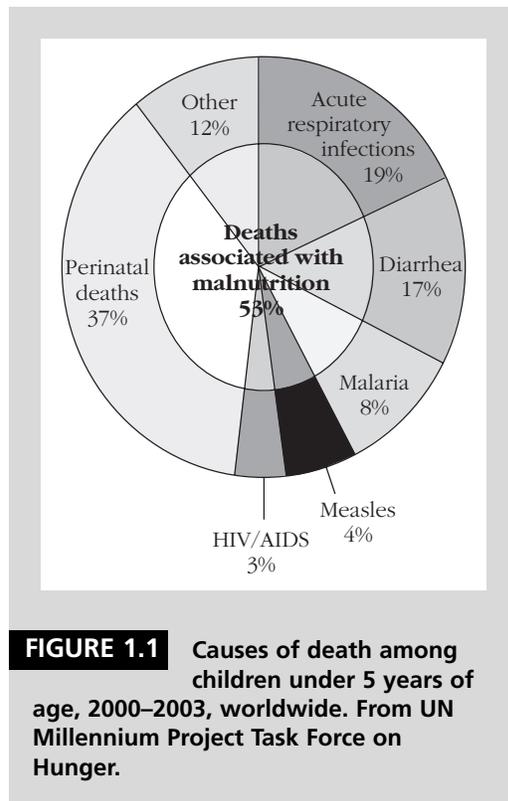
## MALNUTRITION: THE SCALE OF THE PROBLEM

Despite appreciable worldwide improvements in life expectancy, adult literacy, and nutritional status, about 780 million people in developing countries—20% of their combined population—still do not have access to enough food to meet their basic daily needs for nutritional well-being. A review of all available current information on the prevalence of hunger and malnutrition suggest that one of every five persons in the developing world is chronically undernourished, 192 million children suffer from protein-energy malnutrition (PEM), and over 2000 million experience micronutrient deficiencies.

Childhood underweight is internationally recognized as an important public health problem and its devastating effects are well established. It is the direct cause of about 300 000 deaths per year and is indirectly responsible for about half of all deaths in young children; the risk of death is directly correlated with the degree of malnutrition. An epidemiological analysis from 56 devel-

oping countries indicated that 53% of deaths in children 6 to 59 months old were due to malnutrition's potentiating effects in infectious diseases and that mild and moderate malnutrition was involved in 83% of those deaths (Figure 1.1).

Along with this problem, in developing societies are emerging new epidemics of diet-related diseases resulting from the profound demographic changes, urbanization and the economic transition that is transforming and globalizing the food systems in these countries. Thus, many developing countries are facing new and additional challenges of coexisting hunger along with the emergence of other forms of malnutri-



**FIGURE 1.1** Causes of death among children under 5 years of age, 2000–2003, worldwide. From UN Millennium Project Task Force on Hunger.

## KEY POINTS

- Freedom from hunger and malnutrition is a basic human right and its presence is unacceptable in a world that has both the knowledge and the resources to end this human catastrophe.
- Despite worldwide improvements, about 780 million people in developing countries still do not have access to enough food to meet their basic daily needs, 192 million children suffer from protein-energy malnutrition, and over 2000 million experience micronutrient deficiencies.
- Developed countries may encounter a different set of nutritional deficiencies, most often related to alcohol abuse, dietary habits, and impaired absorption of dietary nutrients secondary to intestinal malabsorption syndromes.
- According to WHO data, the prevalence of underweight children demonstrates that it continues to be an enormous problem of public health in developing countries, especially in African and Asian countries.

**KEY POINTS**

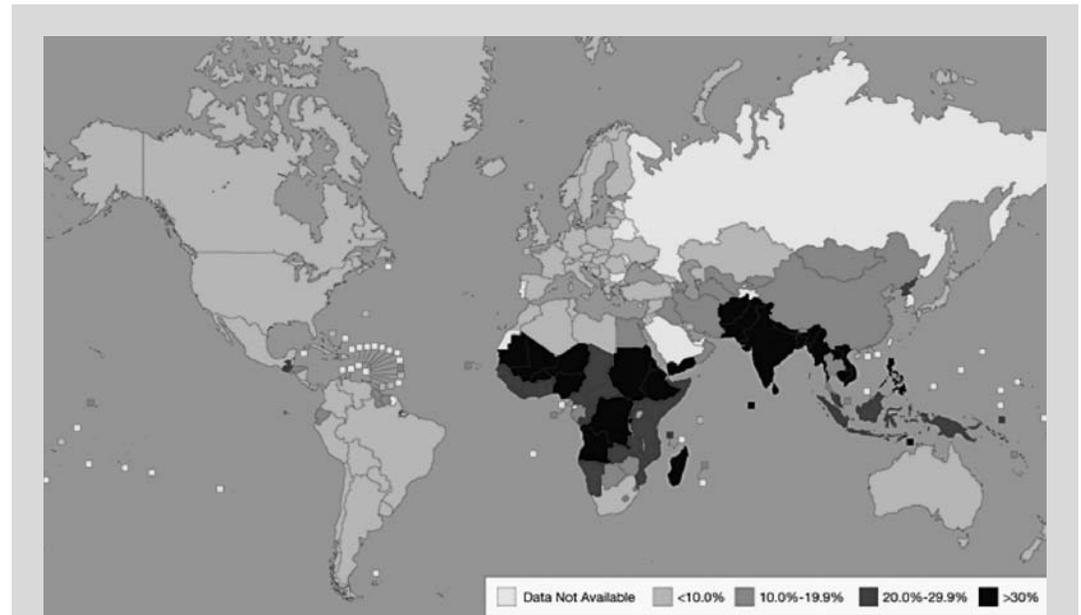
- Added to the malnutrition catastrophe, the burden of chronic, noncommunicable diseases of adults has been added. Many low- and middle-income countries must now respond to both sets of diseases needing responses at global, national, community, and family levels.
- Poverty, ignorance, and disease, coupled with inadequate food supplies and unhealthy environments still persist unchanged as a group of interacting factors which combine to create conditions in which malnutrition flourishes.

tion. In contrast, developed countries may encounter a different set of nutritional deficiencies, most often related to alcohol abuse, dietary habits, and impaired absorption of dietary nutrients secondary to intestinal malabsorption syndromes.

As a basic pillar for social and economic development, the World Health Organization (WHO) has established hunger and malnutrition as targets in the Millennium Development Goals initiative (MDG-2000). Between 1990 and 2015, the specific aims are to halve the prevalence of underweight in children younger than 5 years old and the proportion of the population below the minimum level of dietary energy consumption. So far, the trends to reach the above-mentioned goals are not encouraging, especially because of the deteriorating situation in Africa and Southeast Asia related to the AIDS epidemic, together with the political and social instability experienced in those regions. According to WHO data, the geographical distribution and prevalence of underweight children (which is proportional to global nutritional status) demonstrates that it continues to be an enormous problem of public health in underdeveloped coun-

tries: very high levels of childhood underweight are present in 12 African countries and in 13 Asian countries. (Figure 1.2: Prevalences were categorized as less than 10%, 10% to 19%, 20% to 29%, and 30% or more.)

Malnutrition caused almost 4 million deaths and contributed to many more in the year 2000, most of which occurred in Africa and Southeast Asia, affecting particularly pregnant women and young children. To this human catastrophe, it has been added the burden of chronic, noncommunicable diseases of adults, especially heart disease, stroke, and cancer, which make up approximately 60% of global mortality and almost 50% of the global burden of disease. These conditions are the leading cause of disease burden in all but the African region of WHO. The dual burden of nutritional diseases encompasses both malnutrition and micronutrient deficiencies and the chronic-noncommunicable diseases of adults. The rapidity of the nutritional transition means that many low- and middle-income countries must now respond to both sets of diseases needing responses at global, national, community, and family levels.



**FIGURE 1.2** Geographical pattern of underweight in children younger than 5 years. From the WHO Global Database on Child Growth and Malnutrition.

## NATURE AND EVOLUTION

Social, economical, biological, and environmental factors may be underlying causes for the insufficient intake of foods with proteins of poor nutritional quality that lead to malnutrition. Data from around the world show that the causes underlying most nutrition problems have not changed very much over the past 50 years. Poverty, ignorance and disease, coupled with inadequate food supplies, unhealthy environments, social stress, and discrimination, still persist unchanged as a group of interacting factors which combine to create conditions in which malnutrition flourishes.

The total number of malnourished children has not decreased in past decades because of the rise in population in countries where malnutrition is highly prevalent. As an example, in sub-Saharan Africa, current population growth rates of about 3%—the highest in the world—suggest that the number of malnourished children will continue growing unless the population growth rates are dramatically reduced. The realization that malnutrition is not just a food problem has been appreciated for many years, but the concept of the importance of giving consideration to food, health, education, and care is of more recent origin.

Nevertheless, the absence of poverty does not ensure adequate nutrition: the education level, physical or mental limitations that prevent access to food, religious food preferences, food allergies, food intolerance, and the use of alcohol, illicit addictive drugs and tobacco influence appetite and meal patterns that, as was explained previously, are the reasons that are producing malnutrition in developed countries. Of peculiar importance are the increasingly frequent reports on the raise in the relative risk of developing diseases as stroke, polyneuropathies, and dementia in persons who live under particular lifestyles, such as vegetarian diets, which are clearly related to nutritional deficiencies, especially a deficit of vitamin B<sub>12</sub> and secondary hyperhomocystinemia.

It is possible to subdivide malnutrition into two types or constituents: protein-energy malnutrition and micronutrient deficiencies. A diet that is frequently deficient in macronutrients (protein, carbohydrates and

fat) or micronutrients (minerals and vitamins) could lead to protein-energy malnutrition/specific micronutrient deficiencies, or both.

## PROTEIN-ENERGY MALNUTRITION

Protein-energy malnutrition (PEM) results when the body's needs for protein, energy fuels, or both cannot be satisfied. First descriptions of the disease in the early part of the last century led to the belief that the disease was caused by tropical parasites or a vitamin deficiency. It includes a wide spectrum of clinical manifestations conditioned by the intensity of protein or energy deficit, the severity and duration of the deficiencies, the age of the host, the cause of the deficiency, and the association with other nutritional or infectious diseases.

Dietary energy and protein deficiencies usually occur together, but sometimes one predominates and, if severe enough, may lead to the clinical syndrome of *kwashiorkor* (predominantly protein deficiency) or *marasmus* (mainly energy deficiency). *Marasmic kwashiorkor* is a combination of chronic deficiency and chronic or acute protein deficit. The term “kwashiorkor” was used by the Ga tribe in the Gold Coast (now Ghana) for “the sickness the older child gets when the next baby is born,” and already suggested that the disease could be associated with an inadequate diet during the weaning period. In the 1940s, researchers showed that most patients had low concentrations of serum proteins.

The origin of PEM can be *primary*, when it is the result of inadequate food intake, or *secondary*, when it is the result of other diseases that lead to low food ingestion, inadequate nutrient absorption or use, increased nutritional requirements, and/or increased nutrient losses. After insufficient diet, the next major cause of protein-energy malnutrition is severe and chronic infections, particularly those producing diarrhea, as helminthic infections. A considerable amount of literature, documenting studies both in experimental animals and in people, demonstrates that dietary deficiency diseases may reduce the body's resistance to infections which affects nutritional status in several ways. Perhaps the most important of these is that

## KEY POINTS

- The total number of malnourished children has not decreased in past decades because of the rise in population in countries where malnutrition is highly prevalent.
- Vegetarians can develop nutritional deficiencies, with the subsequent increase in the relative risk of developing diseases such as stroke, dementia, and polyneuropathies.
- Malnutrition can be subdivided into two types of constituents: protein-energy malnutrition and micronutrient deficiencies.
- PEM clinically manifests as predominantly protein deficiency, kwashiorkor, or mainly energy deficiency—marasmus.
- The origin of PEM can be primary, when it is the result of inadequate food intake, or secondary, when it is the result of other diseases that lead to low food ingestion, inadequate nutrient absorption or use, increased nutritional requirements, and/or increased nutrient losses.

**KEY POINTS**

- After insufficient diet, the next major cause of protein-energy malnutrition is severe and chronic infections, particularly those producing diarrhea, as helminthic infections.
- Of all children under the age of 5 years in developing countries, about 31% are underweight, 38% have stunted growth, and 9% show wasting.
- Worldwide, median case fatality of PEM has remained unchanged at 20% to 30% over the past 50 years, but low mortality is attainable with adequate treatment, and in some centers, it is as low as 4% to 6%.
- Micronutrient deficiencies produce typical diseases that improve with the restoration of the nutrients, constitute a risk factor for the development of other diseases and increase the general risk of infectious illness.

bacterial and some other infections lead to an increased loss of nitrogen from the body, probably by an increased breakdown of tissue protein and mobilization of amino acids, especially from the muscles.

PEM can affect all age groups but it is more frequent among infants and young children whose growth increases nutritional requirements, who cannot obtain food by their own means, and who, when living under poor hygienic conditions, frequently become ill with diarrhea and other infections. In children, it is defined by measurements that fall below 2 standard deviations under the normal weight for age (underweight), height for age (stunting), and weight for height (wasting). Wasting indicates recent weight loss, whereas stunting usually results from chronic weight loss. Of all children under the age of 5 years in developing countries, about 31% are underweight, 38% have stunted growth, and 9% show wasting. Pregnant and lactating women can also have PEM because of their increased nutritional requirements as also can the elderly who are unable to care properly for themselves.

**Pathophysiology and Clinical Features**

PEM develops gradually over weeks or months. This allows a series of metabolic and behavioral adjustments that result in decreased nutrient demands and a nutritional equilibrium compatible with a lower level of cellular nutrient availability. The pathological changes include immunological deficiency in the humoral and cellular subsystem from protein deficiency and lack of immune mediators (e.g., tumor necrosis factor). Metabolic disturbances also play a role in impaired intercellular degradation of fatty acids because of carbohydrate deficiency. The poor availability of dietary proteins reduces protein synthesis. Adaptations lead to the sparing of body protein and preservation of essential protein-dependent functions. If the supply of nutrients becomes persistently lower, the patient can no longer adapt and may even die.

*Kwashiorkor* usually manifests with edema, changes to hair and skin color, anemia, hepatomegaly, lethargy, severe immune deficiency and early death (Figure 1.3). *Marasmus* is diagnosed when subcutaneous



**FIGURE 1.3** Kwashiorkor clinical expression. With permission from parents.

fat and muscle are lost because of endogenous mobilization of all available energy and nutrients.

Worldwide, median case fatality of PEM has remained unchanged at 20% to 30% over the past 50 years due to outmoded and faulty case management, with the highest levels (40% to 60%) among those with edematous PEM. Low mortality is attainable with adequate treatment, and in some centers it is as low as 4 to 6% for both edematous and nonedematous forms.

**MICRONUTRIENT DEFICIENCIES**

Micronutrient deficiencies, also sometimes referred to as “the hidden hunger,” are considered a public health problem in developing countries worldwide, particularly vitamin A, iodine, iron, and zinc deficiencies. Nutritional insufficiency occurs when people do not have access to micronutrient-rich foods such as fruit, vegetables, animal products and fortified foods, usually because they are too expensive to buy or are locally unavailable. Micronutrient deficiencies produce typical diseases that improve with the restoration of the nutrients, constitute a risk factor for the development of other diseases, and increase the general risk of infectious ill-

ness; some recent studies have demonstrated that it mimics radiation in that it damages DNA by causing single- and double-strand breaks, oxidative lesions, or both, increasing the risk of cancer.

Nutritional deficiencies rarely occur in isolation, and this may complicate an accurate diagnosis of the different syndromes resulting from vitamin deficiency. It is seen commonly in disorders with impaired absorption of fat-soluble vitamins because of either transport across the intestinal epithelium or intraluminal factors. These disorders include cholestatic liver disease, cystic fibrosis, abetalipoproteinemia, primary biliary cirrhosis, pancreatic insufficiency, short gut syndrome, celiac sprue, and gastrointestinal surgeries.

In individuals with borderline deficiency states, fully developed clinical disease may be brought about by stress associated with chronic infection, hyperemesis of pregnancy, or other acute illnesses. The groups most vulnerable are pregnant women, lactating women, and young children, mainly because they have a greater need for vitamins and minerals and are more susceptible to the harmful consequences of deficiencies.

### CLINICAL AND FUNCTIONAL ASSESSMENT OF MALNUTRITION

Determining the optimal approach to nutritional assessment in the clinical setting is difficult because nonnutritional factors alter many of the parameters used to determine nutritional status. While there is no single irrefutable measure of nutritional status, proficiency in detecting malnutrition in its early stages is essential for effective treatment and prevention of adverse clinical outcomes, and interval assessments of nutritional status are required to evaluate the efficacy of any nutritional intervention.

Nutritional assessment requires integration of the medical history, the physical examination, selected laboratory data, estimation of nutritional requirements, and approaches to nutritional intervention and its outcome. The physiological impairment that accompanies significant weight loss may be the primary cause of increased morbidity and mortality: thus, bedside assessment of functional status may be an important com-

ponent of clinical nutritional assessment. Physiological function is assessed by overall activity, exercise tolerance, grip strength, respiratory function, wound healing, and plasma albumin concentration.

### HIV AND NUTRITION

Perhaps no disease has a more dramatic and obvious effect on nutritional status than acquired immunodeficiency syndrome (AIDS), the disease caused by the human immunodeficiency virus (HIV). There is no doubt that the disease and its associated opportunistic infections cause marked anorexia, diarrhea and malabsorption as well as increased nitrogen losses. HIV infection has become increasingly prevalent globally, with more than 40 million infected individuals worldwide, the majority of whom live in the resource-limited world, especially sub-Saharan Africa and Asia.

In some countries, there is a huge concern for the growth and development of children with AIDS. Comparing data from different studies on the nutritional status on young children in Africa, there has been observed a significant increase in the stunting rates: in 1988, stunting was found in 28% of children less than 5 years of age, whereas it has actually increased to 54%. In addition, malnutrition has been associated with rapid disease progression, an increased risk of transmission of HIV from infected mothers to infants, and may further compromise HIV-infected individuals who have tuberculosis or persistent diarrheal disease. The introduction of highly active antiretroviral therapy may have a significant impact on the mortality of HIV, but will not alleviate the malnutrition associated with HIV infection in the global setting. Because of this, HIV-positive people should adopt a sensible balanced diet and consult an experienced nutrition specialist for individualized recommendations.

### NUTRITION AND DISEASES OF THE NERVOUS SYSTEM

**Nutrition and Nervous System Development** During the period from conception until the third year of postnatal life, the brain grows at a rate unmatched by any later developmental stage. Although this sequence of events is guided largely by

### KEY POINTS

- Nutritional deficiencies are seen commonly in malabsorption syndromes such as cholestatic liver disease, cystic fibrosis, abetalipoproteinemia, primary biliary cirrhosis, pancreatic insufficiency, short gut syndrome, celiac sprue, and gastrointestinal surgeries.
- Nutritional assessment requires integration of the medical history, the physical examination, selected laboratory data, estimation of nutritional requirements, and approaches to nutritional intervention and its outcome.
- No disease has a more dramatic and obvious effect on nutritional status than AIDS, and malnutrition has been associated with rapid disease progression and an increased risk of transmission of HIV from infected mothers to infants, and may further compromise individuals who have tuberculosis or persistent diarrheal disease.

**KEY POINTS**

- Although brain growth is guided largely by genes, it also depends on an adequate gestation period and the availability of oxygen, protein, energy, and micronutrients as well as, after birth, sensory stimulation, activity, and social interaction.
- The period between conception and age 3 years is regarded as a “sensitive period” when the brain is susceptible to experiences that can assist or hinder cognitive development.
- Undernutrition during pregnancy has been linked with poor birth outcomes, including low birth weight, smaller head circumference, and brain weight than healthy newborns. The longer nutritional deprivation continues, the greater the effect on the brain.
- Factors that can determine developmental outcome include the severity, timing, and duration of nutritional deprivation; the quality of nutritional rehabilitation; and the degree of family stimulation and psychosocial support.
- Nutritional deficiencies may result in a variety of disorders that affect either the peripheral nervous system (PNS) or central nervous system (CNS). More commonly, both are affected simultaneously.

genes, the early development of the brain does not simply represent the unfolding of a rigidly deterministic, genetic program. Rather, the child’s environment plays an important role from the earliest stages of development, with the potential to assist or disrupt the process. Normal brain development depends on an adequate gestation period and the availability of oxygen, protein, energy, and micronutrients as well as, after birth, sensory stimulation, activity, and social interaction.

Alternatively, development can be thrown off course by the absence of these conditions or by exposure to toxic substances such as alcohol, lead, or tobacco, prenatal infections, metabolic abnormalities, or chronic stress. The extent of damage wrought by environmental assaults depends largely on timing; that is, the coincidence of deprivation or exposure to adversity with the growth spurt of a particular organ. Given the rapid rate of brain growth, the period between conception and age 3 years is regarded as a “sensitive period” when the brain is susceptible to experiences that can assist or hinder cognitive development.

**Effects of Malnutrition** Undernutrition during pregnancy (measured by low maternal weight-for-height and low weight gain during pregnancy) has been linked with poor birth outcomes, including low birth weight, smaller head circumference and brain weight than healthy newborns. Studies have also identified a relationship between these birth outcomes and later cognitive delays. Although the precise mechanisms by which poor nutrition affects the brain are not fully understood, it is thought that, in general, the longer nutritional deprivation continues, the greater the effect on the brain. About potential of recovery, the beneficial effects of breast-feeding for the cognitive development of premature and low birth weight infants are especially pronounced. Pediatricians are in agreement that breast milk contains specific nutrients, such as fatty acids, which cannot be found in formula milk, and randomized clinical trials confirm the importance of these nutrients for vulnerable infants. In one study, researchers compared premature infants (with birth weights <1.8 kg) who were fed with breast milk with those who received

infant formula. When followed up 8 years later, the IQ scores of children who had received breast milk were 8.3 points higher on average than those who had been fed with formula milk only.

At latter years, children who suffer severe PEM also may have decreased brain growth and neurotransmitter production, and impaired nerve myelination with diminished velocity of nerve conduction. Cellular elements more commonly affected by nutritional deficiency include the neuron itself and the myelin sheath. In deficiency states that affect the neuron, the axon usually shows the first signs of damage and will be most severely affected. The distal ends of longer axons are affected first, since they are most susceptible to nutritional deprivation. With continued deprivation, the process moves toward the cell body. There may be axonal degeneration as well as demyelination.

Factors that can determine developmental outcome include the severity, timing, and duration of nutritional deprivation; the quality of nutritional rehabilitation and psychosocial support; the degree of family stimulation; and a host of positive and negative environmental factors. Stimulation is particularly important during this period as synapses are eliminated selectively according to whether connections have been made. Poor nutrition specifically affects behavioral and neurologic function through its adverse impact on myelination, which produces a lack of development of cognitive and motor skills.

**Neurologic Disorders** Nutritional deficiencies may result in a variety of disorders that affect either the peripheral nervous system (PNS) or central nervous system (CNS). More commonly, both are affected simultaneously. Nutritional diseases of the nervous system have been carefully studied for more than 100 years, and many that were common in the last century now occur infrequently in developed countries. In the 1800s, beriberi occurred in epidemic proportions throughout the world. Similarly, pellagra was once common in the southern United States, but since 1940 the incidence has greatly diminished as a result of supplementing bread with niacin as well as major improvements in the overall diet of the

affected population. In some Third World countries, pellagra and beriberi remain common, and these as well as other nutritional deficiencies continue to be a major cause of disease. With the advent of new technologies, every day more neurologic syndromes related to micronutrient deficiencies are described, which increases the potential functional recovery of patients given the reversibility of the neurologic manifestations if treatments are used promptly (Table 1.1).

**Alcoholism-related Nutritional Neurologic Disorders** Alcoholism remains one of the major causes of nutritional deficiencies in the world. The interaction between nutrition and alcoholism occurs at many levels and is complex. Alcoholic beverages contain calories but almost no other useful constituents. Ethanol-containing beverages alter appetite and affect food intake and use. It alters the storage, mobilization, activation, and metabolism of nutrients.

Alcoholics tend to have clinical or laboratory signs of soluble vitamin insufficiency correlated with the increasing amount of alcohol they drink and a corresponding decrease in vitamin intake. Chronic alcohol consumption can result in vitamin deficiency by causing inadequate nutritional intake, decreased absorption from the gastrointestinal tract, and impaired utilization in the cells. This is true for thiamine, riboflavin, pyridoxine, folic acid, and ascorbic acid. Logically having diminished the capacity of concentration of biliary salts in the intestinal lumen, of equal form, it limits the absorption of the fat-soluble vitamins (A, D, E, K). For these reasons, it is in chronic alcoholics where we frequently find several of the neurologic syndromes associated with nutritional deficiencies (Table 1.2).

*Thiamine (B<sub>1</sub>)* Also known as vitamin B<sub>1</sub>, thiamine was first discovered in Japan when researching how rice bran cured patients of

**KEY POINT**

- Alcoholism remains one of the major causes of nutritional deficiencies in the world. Chronic alcohol consumption can result in vitamin deficiency by causing inadequate nutritional intake, decreased absorption from the gastrointestinal tract, and impaired utilization in the cells.

**TABLE 1.1** Classification of Malnutrition-related Neurologic Disorders

Micronutrient Deficiency	Neurologic Disorder
Thiamine (B1)	Encephalopathy: Wernicke-Korsakoff Syndrome, Nonalcoholic Cerebellar Degeneration, Peripheral Neuropathy, Cranial Nerves Neuropathy (occasional)
Niacin (B3)	Pellagra: Dementia, Startle Myoclonus, Myelopathy?/ Neuropathy?
Pyridoxine (B6)	Polyneuropathy, Infantile Seizures, Pyridoxine- Responsive Confusional State, Depression Hyperhomocystinemia/Stroke?
Cobalamin (B12)	Subacute Combined Degeneration (SCD) of Spinal Cord, Polyneuropathy/Optic Neuropathy Reversible Leukoencephalopathy: Cognitive Impairment, Hyperhomocystinemia/Stroke Mental Retardation (in children) Neural Tube Defects?
Zinc	Dyslexia?, Myelopathy/Neuropathy?, Infantile Tremor Syndrome?
Magnesium	Stroke, Hypomagnesemia-related Seizures, Parkinsonism-Dementia Complex?
Iodine	Cretinism-Endemic Mental Retardation
Copper	Myelopathy Peripheral Neuropathy
Folate	Neural Tube Defects, Cerebral Folate Deficiency Syndrome/ Autism/Optic Neuropathy Hyperhomocystinemia: Stroke, Dementia
Vitamin A	Night Blindness/Keratomalacia
Vitamin E	Sensory Polyneuropathy, Spinocerebellar Degeneration/ Dementia

**KEY POINTS**

- Wernicke disease refers to a neurologic disorder characterized by a classic triad of ophthalmoplegia, gait ataxia, and confusion.
- Korsakoff psychosis refers to an amnesic state in which there is severe impairment of short-term memory and confabulation.
- Only 20% of cases may be recognized during life. Only 16% of patients exhibit the classic triad, and as many as 19% may have no clinical signs.
- WKS should be considered a neurologic emergency. It must be treated promptly with 100 mg of thiamine given intravenously before starting dextrose infusion and periodically thereafter.
- Cerebellar degeneration is a syndrome usually seen in undernourished alcoholic patients secondary to atrophy of the anterior and posterior cerebellar vermis.

**TABLE 1.2** Alcoholism-related Nutritional Neurologic Disorders

Wernicke-Korsakoff Syndrome
Alcoholic Polyneuropathy
Alcoholic Myopathy
Alcoholic Myelopathy?
Pellagra
Alcoholic Cerebellar Degeneration
Marchiafava-Bignami Disease
Alcoholic Dementia

beriberi. It plays an important role in helping the body convert carbohydrates and fat into energy, being a cofactor required by three enzymes involved in two pathways of carbohydrate metabolism. It is essential for normal growth and development and helps to maintain proper functioning of the heart and the nervous and digestive systems. Systemic thiamine deficiency can lead to myriad problems including neurodegeneration, wasting, and death.

One of the best-known neurologic syndromes caused by thiamine deficiency is *Wernicke-Korsakoff syndrome*. Wernicke disease refers to a neurologic disorder characterized by a classic triad of ophthalmoplegia, gait ataxia, and confusion. Other symptoms may be hypotension, hypothermia, cardiac failure, and coma. Korsakoff psychosis refers more specifically to an amnesic state in which there is severe impairment of short-term memory and confabulation. Wernicke disease is specific to thiamine deficiency, whereas Korsakoff psychosis may be seen in association with other disorders of the nervous system. In the category of micronutrient deficiencies, those two entities should actually be considered together. They often occur simultaneously in alcoholism and other states of nutritional deprivation in which thiamine reserves are exhausted. Only 20% of cases may be recognized during life. Only 16% of patients exhibit the classic triad, and as many as 19% may have no clinical signs.

In the hospital setting, Wernicke-Korsakoff syndrome (WKS) can be precipitated in those with borderline thiamine defi-

ciency by administration of intravenous fluid containing dextrose. Since metabolism of sugars and carbohydrates requires thiamine as a cofactor, the frank deficiency state can be precipitated with dextrose.

In the neuropathological appearance of WKS, there are necrosis of both neuronal and oligodendroglial elements in the mammillary bodies, superior cerebellar vermis, and hypothalamus. Petechial hemorrhages are frequently seen in the mammillary bodies and periaqueductal gray. WKS should be considered a neurologic emergency. It must be treated promptly with 100 mg of thiamine given intravenously before starting dextrose infusion and periodically thereafter. The ocular manifestations may begin to resolve as early as 6 hours after administration of thiamine. The ataxia and confusional state may also improve following thiamine administration, but memory deficits are likely to persist.

Diencephalic regions and, in particular, the cerebellum demonstrate lesions in cases of prolonged thiamine deficiency, such as that observed in alcohol-dependent individuals or in patients with cancer or AIDS. *Cerebellar degeneration* is a syndrome usually seen in undernourished alcoholic patients but it also has been observed in nutritionally deprived nonalcoholics, especially with thiamine deficiency. This disorder

**CASE 1: WERNICKE-KORSAKOFF SYNDROME**

A 30-year-old female patient, after abdominal surgery, was treated for a prolonged time with high glucose concentration total parenteral nutrition. In the postoperative period, the patient showed severe encephalopathy with ataxia, ophthalmoplegia, and stupor. We prescribed IV thiamine, and she recovered dramatically from her consciousness disorder. However, she progressed to a Korsakoff syndrome with memory and cognitive defects. Thiamine deficiency is a reemerging problem in nonalcoholic patients and it may develop in surgical patients with risk factors such as malnutrition, prolonged vomiting, and long-term high glucose concentration parenteral nutrition.

usually presents with wide-based gait and truncal ataxia. Pathologically there is severe atrophy of the anterior and posterior cerebellar vermis. The reasons why the cerebellum may be sensitive to this type of insult it still unknown.

*Neuropathic beriberi* is a degenerative disorder of the peripheral nerves and was described in the late nineteenth century. The symptomatology is diverse, many patients are asymptomatic, and evidence of peripheral nerve affection is found only on clinical or electromyographic examination. The majority of patients, however, are symptomatic: weakness, paresthesias, and pain being the usual complaints. The symptoms are insidious in onset and slowly progressive, but occasionally they seem to evolve or to worsen rapidly over a matter of days. The initial symptoms are usually referred to the distal portions of the limbs and progress proximally if the illness remains untreated. More often some aspect of motor disability constitutes the chief complaint, but in about one-quarter of the patients, the main complaints are pain and paresthesias.

The essential pathological change is one of axonal degeneration, with destruction of both axon and myelin sheath. Segmental demyelination may also occur, but only in a small proportion of fibers. The most pronounced changes are observed in the distal parts of the longest and largest myelinated fibers in the crural and, to a lesser extent, brachial nerves. Anterior horn and dorsal root ganglion cells undergo chromatolysis, indicating axonal damage. The degenerative changes in the posterior columns seen in some cases are probably secondary to the changes in the dorsal spinal roots.

The first treatment consideration is to supply adequate nutrition in the form of a balanced diet supplemented with B vitamins. Aspirin or acetaminophen is usually sufficient to control hyperpathia; occasionally, codeine in doses of 15 to 30 mg must be added. Some patients with severe burning pain had been helped temporarily by blocking the lumbar sympathetic ganglia or by epidural injection of analgesics. Recovery from nutritional polyneuropathy is a slow process. In the mildest cases there may be a considerable restoration of motor function in

a few weeks. In severe forms of the disease, several months may pass before the patient is able to walk unaided.

*Niacin (B<sub>3</sub>)* Also known as nicotinic acid or vitamin B<sub>3</sub>, niacin is a water-soluble vitamin whose derivatives such as NADH, NAD, NAD<sup>+</sup>, and NADP play essential roles in energy metabolism in the living cell and DNA repair. Severe lack of niacin causes the deficiency disease *pellagra*, whereas a mild deficiency slows down the metabolism decreasing cold tolerance. Pellagra incidence has diminished greatly because of the general practice of enriching bread with niacin. Nevertheless, among the vegetarian, maize-eating people of underdeveloped countries and among the black population of South Africa, pellagra is still a common disease; in developed countries, is practically confined to alcoholics.

In its fully developed form, pellagra affects the skin, alimentary tract, and hematopoietic and nervous systems. The early symptoms may be mistaken for those of a neurosis: insomnia, fatigue, nervousness, irritability, and feelings of depression are common complaints. Examination may disclose mental dullness, apathy, and an impairment of memory. Sometimes an acute confusional psychosis dominates the clinical picture. Untreated, these symptoms may progress to a *dementia*. The dermatological feature, often permitting one to make a confident diagnosis, is a scaly dermatitis in sun-exposed areas. Diarrhea and glossitis or other forms of mucous membrane disorder may be accompaniments (dementia-dermatitis-diarrhea triad).

The spinal cord manifestations have not been clearly described; in general, the signs of *myelopathy* are referable to both the posterior and lateral columns, predominantly the former. Signs of *peripheral neuropathy* are relatively less common and are indistinguishable from those of neuropathic beriberi.

It is known that pellagra may result from a deficiency of either nicotinic acid or tryptophan, the amino acid precursor of nicotinic acid. One milligram of nicotinic acid is formed from 60 mg of tryptophan, a process for which pyridoxine is essential. The relationship of niacin to tryptophan metabolism

#### KEY POINTS

- Neuropathic beriberi is a degenerative disorder of the peripheral nerves that produces weakness, paresthesias, and pain, usually in the distal portions of limbs.
- Pellagra has diminished greatly because of the general practice of enriching bread with niacin. Nevertheless, among the vegetarian, maize-eating people of underdeveloped countries and among the black population of South Africa, pellagra is still a common disease; in developed countries, it is practically confined to alcoholics.
- Clinically, it is recognize for a classic triad: dementia-dermatitis-diarrhea.
- Other neurologic syndromes related to niacin deficiency are peripheral neuropathy and myelopathy.

**KEY POINTS**

- Pyridoxin-related polyneuropathy generally is a complication of treatment with isoniazid and hydralazine.
- Recent experimental studies have indicated that pyridoxine may directly influence platelet adhesion and cholesterol metabolism, constituting an independent risk factor for stroke.
- Regardless of the cause, cobalamin deficiency should be considered a serious condition; the cause must be investigated, and supplementation should be initiated promptly lest irreversible damage to the CNS continues to progress.

explains the frequent occurrence of pellagra in persons who subsist mainly on corn, which contains only small amounts of tryptophan and niacin. It should be pointed out that only the dermal, gastrointestinal, and neurasthenic manifestations respond to treatment with niacin and tryptophan; neurologic disturbances in pellagrins have proved to be recalcitrant to prolonged treatment with nicotinic acid, although the peripheral nerve disorder may subsequently respond to treatment with thiamine.

*Pyridoxine (Vitamin B<sub>6</sub>)* Pyridoxine assists in the balancing of sodium and potassium as well as promoting red blood cell production. It is linked to cancer immunity and helps fight the formation of homocysteine. It is required for the production of the monoamine neurotransmitters serotonin, dopamine, norepinephrine (noradrenaline) and epinephrine (adrenaline) as it is the cofactor for the enzyme aromatic acid decarboxylase. This enzyme is responsible for converting the precursors 5-hydroxytryptophan (5-HTP) into serotonin and 3,4-dihydroxyphenylalanine (L-dopa) into dopamine, norepinephrine, and epinephrine.

A special type of *nutritional polyneuropathy* is encountered in tuberculous patients as a complication of treatment with isoniazid (INH).

In the recent past, a similar neuropathy was observed in hypertensive patients treated with hydralazine. The neuropathy is characterized by paresthesias and burning pain of the feet and legs, followed by weakness of these parts and loss of ankle reflexes. The nature of INH-induced neuropathy was clarified by Biehl and Volter. They found that the administration of isoniazid results in a marked excretion of pyridoxine and that the administration of pyridoxine in conjunction with INH prevented the development of neuropathy. As a result of this simple preventive measure, very few examples of INH-induced neuropathy are now observed. Pyridoxine deficiency-related polyneuropathy is extremely rare in the absence of these medications.

Pyridoxine deficiency occasionally occurs in newborns. In infants, this is associated with hyperirritability and seizures. There is a

familiar syndrome in which *seizures due to pyridoxine deficiency* appear at birth or shortly later. The seizures respond to supplementation with pyridoxine. The dose required to control seizures is 15 mg/day.

Following early descriptions of atherosclerosis in pyridoxine-deficient monkeys, epidemiological studies have reported an association between low vitamin B<sub>6</sub> and vascular disease. As *hyperhomocystinemia* is frequently encountered in individuals with low pyridoxine, it was suggested that this was the primary mechanism of vascular injury, especially *stroke*. However, recent experimental studies have indicated that pyridoxine may directly influence platelet adhesion and cholesterol metabolism. Alternatively, low vitamin B<sub>6</sub> may be a marker of inflammation, which may promote atherosclerosis.

*Cobalamin (B<sub>12</sub>)* This is one of the most commonly encountered isolated deficiency states in clinical practice. Vitamin B<sub>12</sub> is naturally found in foods including meat (especially liver and shellfish), eggs, and milk products.

Cobalamin deficiency occurs in a variety of clinical settings (Table 1.3). At times, the cause may not be readily apparent. Regardless of the cause, it should be considered a serious condition; the cause must be investigated and supplementation should be initiated promptly lest irreversible damage to the CNS continues to progress.

The clinical manifestations of cobalamin deficiency are referable to disorders of both CNS and PNS myelin. The earliest manifestation is often tingling and paresthesias in the lower extremities. This is accompanied by a pin-and-needles sensation and the perception of muscle weakness. These early symp-

**TABLE 1.3 Etiology of B<sub>12</sub> Deficiency**

<p>Pernicious anemia                  Celiac sprue                  Gastric or ileal resection                  Fish tapeworm infestation                  Inadequate diet</p>
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toms may be due to demyelination in either the peripheral nerves—*peripheral neuropathy*—or the sensory tracts of the spinal cord. As the disease state progresses, patients typically develop a spastic paraparesis with weakness and greatly increased muscle tone in the lower extremities. At this stage, neurologic examination reveals hyperactive reflexes, muscle weakness, loss of vibration and position sense, extensor plantar responses, and impaired bowel and bladder functions. Symptoms that occur at this stage of the illness are due to demyelination in the posterior and lateral columns of the spinal cord—*subacute combined degeneration*.

Neuropsychiatric manifestations may include irritability, apathy, somnolence, excessive fatigue, suspiciousness or paranoia, emotional instability, confusional states, psychosis, and cognitive decline. These symptoms are due to demyelination in the deep white matter of the cerebral hemispheres—*reversible leukoencephalopathy*. In addition, patients may also complain of visual loss accompanied by central scotomas, and on examination, visual acuity is decreased. In late cases, there is bilateral optic atrophy. Prior to any clinical manifestations, evidence of demyelination in the optic nerves may be detected by visual evoked potentials—*optic neuropathy*. Since cobalamin is necessary for conversion of homocysteine to methionine, homocysteine levels may also be elevated, which is a risk factor for stroke and other vascular diseases, especially atherosclerotic disease.

Abnormal vitamin B<sub>12</sub> metabolism occurs in infants born from cobalamin-deficient vegetarian mothers, generally under prolonged exclusive breast-feeding, or those with hereditary diseases, including the Imerslünd-Grasbeck syndrome (cublin mutation resulting in decreased cobalamin transport from the intestinal lumen), transcobalamin II deficiency, and intracellular cobalamin abnormalities. Symptoms become prominent after exhaustion of vitamin B<sub>12</sub> stores acquired in utero. Infants present with *developmental delay*, failure to thrive, lethargy, poor feeding, mental retardation, seizures, listlessness, irritability, ataxia, hyperreflexia, hypotonia, pathologic reflexes, coma, tremor, and myoclonus. The latter may worsen transient-

ly upon initiation of treatment. In addition, there seems to be a moderate association between low maternal B<sub>12</sub> status and the risk of fetal *neural tube defects*.

The diagnosis of vitamin B<sub>12</sub> deficiency is usually suggested by the presence of low serum vitamin B<sub>12</sub> levels (<200 pg/mL). If low serum levels of vitamin B<sub>12</sub> are found, a Schilling test is indicated to determine whether absorption is impaired. In confirmed vitamin B<sub>12</sub> deficiency, treatment should be undertaken as soon as possible regardless of the cause. This should be initiated with intramuscular administration of 1 mg of vitamin B<sub>12</sub> daily for 7 days followed by 1 mg intramuscularly weekly for 1 month. Large doses of B<sub>12</sub> are required to replace tissue stores that have been depleted over a long period. Treatment should be continued with once-monthly injections of vitamin B<sub>12</sub> for the remainder of the patient's life if the underlying cause cannot be overcome. The response to treatment depends mostly on the duration of symptoms prior to diagnosis.

**Zinc** Zinc is an essential element necessary for sustaining all life. Phytates, which are found in whole grain breads, cereals, legumes, and other products, have been known to decrease zinc absorption. Zinc deficiency results from inadequate intake of zinc or inadequate absorption of zinc into the body. Obtaining a sufficient zinc intake during pregnancy and in young children is a real problem, especially among those who cannot afford a good and varied diet. Signs of zinc deficiency include hair loss, skin lesions, diarrhea, wasting of body tissues, and, eventually, death. Brain development is stunted by zinc insufficiency in utero and in youth. Eyesight, taste, smell, and memory are also connected with zinc deficiency.

The neurologic complications of zinc deficiency are not completely established yet. It has been involved in diverse neurologic syndromes like *infantile tremor syndrome*, *myeloneuropathies*, and even *dyslexia*, in which there has been some therapeutic response to the administration of this micronutrient, deducing a causative role. Infantile tremor syndrome is characterized by coarse tremors, mental and physical retardation, light-colored brown hair, skin pigmentation, and anemia.

#### KEY POINTS

- Vitamin B<sub>12</sub> deficiency produces various neurologic syndromes such as myelopathy, neuropathy, leukoencephalopathy, and also an increase in homocysteine levels, which is a risk factor for vascular atherosclerotic disease.
- Abnormal vitamin B<sub>12</sub> metabolism occurs in infants born from cobalamin-deficient vegetarian mothers or those with hereditary diseases; infants present with developmental delay, seizures, hypotonia and they are also at risk of neural tube defects.
- The neurologic complications of zinc deficiency are not completely established yet. It has been involved in diverse neurologic syndromes like infantile tremor syndrome, myeloneuropathies, and even dyslexia.

## KEY POINTS

- Amighi et al. (2004) demonstrated that hypomagnesemia below <0.76 mmol/L exhibited a 3.29-fold increased adjusted risk for neurologic vascular events, favoring magnesium substitution therapy in those patients with advanced atherosclerosis as part of a secondary prevention program.
- Isolated and idiopathic hypomagnesemia is a rare familial condition that is known to present as generalized motor seizures in children. The exact pathophysiology is not known but may relate to disinhibition of specific types of glutamate receptors.

*Magnesium* Magnesium (Mg) ion is essential to the basic nucleic acid chemistry of life, and thus is essential to all cells of all known living organisms. Many enzymes require the presence of magnesium ions for their catalytic action, especially enzymes utilizing ATP, or those which use other nucleotides to synthesize DNA and RNA. It modulates vasomotor tone, blood pressure, and peripheral blood flow.

Magnesium deficiency it has been shown to trigger vasoconstriction and enhance vascular endothelial injury, thus promoting the development and progression of atherosclerosis and latter of secondary *cerebrovascular disease*. Amighi et al. (2004) demonstrated that hypomagnesemia below <0.76 mmol/L exhibited a 3.29-fold increased adjusted risk for neurologic vascular events, favoring magnesium substitution therapy in

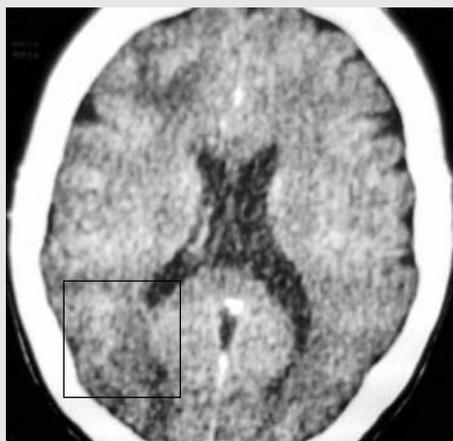
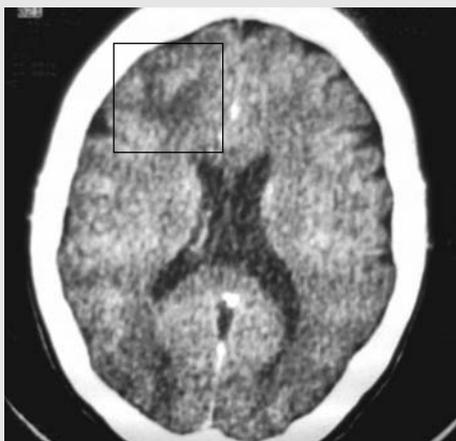
those patients with advanced atherosclerosis as part of a secondary prevention program.

It has also been proposed that Mg deficiency is involved in the pathogenesis of *parkinsonism–dementia complex* (PDC) based on Guam population observations. In this region, this disease had a very high prevalence between 1950 and 1965 but decreased dramatically after 1965. It is thought that drinking water containing low levels of magnesium was involved in the pathogenesis of these diseases. In recent animal models a significant loss of dopaminergic neurons was identified exclusively in the substantia nigra in 1-year-old rats that had been exposed continuously to low Mg intake, which suggests that low magnesium intake may be involved in the pathogenesis of substantia nigra degeneration in humans.

#### CASE 2: VITAMIN B<sub>12</sub> DEFICIENCY

A 44-year-old woman came to the hospital with a history of approximately 1 year of having epigastric burning that was relieved with alkaline agents. Her nutritional condition was deteriorating because of the pain, and she had lost nearly 50 pounds. For 6 months she had perceived fatigue, debility, and progressive pallor. She was hospitalized four times in a regional hospital for anemic syndrome without a diagnostic conclusion. For 3 months she felt a sensation of numbness in her feet, especially on the left side, tending to radiate up to the knees. A week later, she presented with behavioral abnormalities characterized by fluctuating disorientation, drowsiness, visual hallucinations, and apathy. Progressively, relatives noticed short memory defects, and sometimes the patient complained of "dark vision." Two weeks ago, she presented with progressive weakness in both legs with difficulty in the ability to stroll. Simultaneously, the sensation of numbness extended to both hands and she developed urinary incontinence. She denies back pain, dorsal traumas, or another symptomatology. Owing to neurologic symptomatology, she is brought for medical specialized evaluation. On physical examination, the patient seems chronically ill, with extensive zones of alopecia, and she was tachycardic and extremely pale. Neurologically, she was bradyphrenic, inattentive, with temporal-spatial disorientation, marked alteration in planning and execution and secondary short verbal memory impaired. Her Folstein Mini-Mental (MM) Score was 19/30. At cranial nerves she had a visual acuity of 20/400 and the rest were normal. Evaluation of muscle strength showed a marked paraplegia with bilateral hyperreflexia and a positive Babinski sign of left predominance. She presents bilateral hypoesthesia in C7-T1 and L4-S1, arthroanesthesia, statoagnosia and apalesthesia in the lower extremities. She had positive grasp and sucking reflexes. Hoffman and Tromner signs were also positive bilaterally. Lab Studies: CBC: Hb: 8.7 gr/dL, Hto: 25.2 vol%; MCV: 111; MCH: 35.2; MCHC: 34.7; platelets: 365,000; coagulation test were normal; glucose: 112 mg/dL; BUN: 17; creatinine: 0.7; sodium: 136; potassium: 3.4; total bilirubin: 0.82; TSGO: 54; TSGP: 28; total proteins: 7.0 g/dL; LDH: 628 U/L; B<sub>12</sub>: <100 pg/mL (NV 193-982); folate: 15.2 ng/mL (NV 3-17); ferritin: >1500 ng/mL (NV 6-159); thyroid and immune profile were also normal; HIV-ELISA was negative. Smear of peripheral blood showed evidence of macrocytosis, with segmented cores. CSF analysis did not show abnormalities. CT scan revealed multifocal hypodensities in the bilateral frontal corticosubcortical region of vascular characteristics and another hypodensity at the right occipital lobe, predom-

inantly in the white matter, without perilesional edema, not involving a specific arterial territory neither enhancing with intravenous contrast. The electrophysiological studies confirmed the presence of a chronic symmetrical polyneuropathy with severe axonal damage, affecting mainly the lower members. Somatosensory evoked potentials (SSEPs) showed signs of axon-myelinic commitment of the bilateral tibial nerve. It was not possible to specify with accuracy the existence of posterior cordal commitment in the SSEPs due to the important peripheral commitment of bilateral tibial nerves. Gastrointestinal endoscopy and biopsy results in the appraisal of gastric mucus with chronic inflammation signs in the lamina propria and intestinal metaplasia. It was concluded that the patient had a cobalamin ( $B_{12}$ ) deficiency in relation to a probable pernicious anemia (it was not possible to perform a Schilling test or autoantibody studies) with the posterior development of nutritional leukoencephalopathy, optical neuropathy, subacute combined degeneration of the spinal cord, cerebrovascular disease probably due to hyperhomocystinemia (it was not measured), and a sensitive polyneuropathy of distal predominance. Vitamin  $B_{12}$  therapy was initiated, and 4 weeks later she obtained 24/30 at Folstein MM, recovered visual acuity until 20/40 bilaterally but showed little improvement on motor function (-2/5). She continues monthly therapy with vitamin  $B_{12}$  and is undergoing rehabilitation.



Isolated and idiopathic hypomagnesemia caused by defective renal reabsorption of magnesium is a rare familial condition with variable inheritance. Is a rare condition that is known to present as generalized motor seizures in children. The exact pathophysiology of *hypomagnesemic seizures* is not known but may relate to disinhibition of specific types of glutamate receptors.

**Iodine** Iodine deficiency (ID) is the greatest cause of preventable *mental retardation* in the world. Globally at least 800 million people live in iodine-deficient environments which make them susceptible to endemic goiter, cretinism, mental deficiency, decreased fertility, and perinatal and infant deaths. Although most of the affected people live in developing countries, it has been estimated that at least 11% of the population

in Europe are suffering from subclinical ID.

The most important target groups for the effects of iodine deficiency from a public health point of view are pregnant mothers, fetuses, neonates, and young infants because the brain damage resulting in irreversible mental retardation, is the consequence of thyroid failure occurring during pregnancy, fetal, and early postnatal life. The main cause of endemic goiter and cretinism is an insufficient dietary supply of iodine. The additional role of naturally occurring goitrogens has been documented in the case of certain foods (milk, cassava, millet, nuts) and bacterial and chemical water pollutants. The most serious complication of iodine deficiency is *endemic cretinism*, a syndrome characterized by irreversible mental retardation together with

#### KEY POINT

- Iodine deficiency (ID) is the greatest cause of preventable mental retardation in the world. Although most of the affected people live in developing countries, it has been estimated that at least 11% of the population in Europe are suffering from subclinical ID.

**KEY POINTS**

- Endemic cretinism is a syndrome characterized by irreversible mental retardation together with either a predominant neurologic syndrome or predominant hypothyroidism, or a combination of both syndromes.
- The most common neurologic manifestations of copper deficiency are myelopathy, peripheral neuropathy, and optic neuritis.
- Folic acid is very important for all women who may become pregnant. Adequate folate intake during the periconceptual period helps protect against a number of congenital malformations including neural tube defects.
- Taking 400 mcg of synthetic folic acid daily from fortified foods and/or supplements has been suggested, and this could potentially reduce the risk of neural tube defects as much as 48%.
- Cerebral folate deficiency is a neurologic syndrome that develops 4 to 6 months after birth, characterized by irritability, slow head growth, psychomotor retardation, cerebellar ataxia, pyramidal tract signs in the legs, dyskinesias (e.g., choreoathetosis and ballismus), and, in some cases, seizures and autism.
- Low concentrations of folate may increase levels of homocysteine, which is a risk factor for stroke and dementia.

either a predominant neurologic syndrome or predominant hypothyroidism, or a combination of both syndromes. This makes a strong case for a policy on universal salt iodization, which is a simple and cheap measure.

**Copper** Copper is essential in all higher plants and animals. Copper is carried mostly in the bloodstream on a plasma protein called ceruloplasmin. Copper is found in a variety of enzymes, including the copper centers of cytochrome c oxidase and the enzyme superoxide dismutase. In recent years the neurologic manifestations of acquired copper deficiency in humans have been recognized. The most common manifestation is that of a *myelopathy* presenting with a spastic gait and prominent sensory ataxia. Central nervous system (CNS) demyelination, *peripheral neuropathy*, and *optic neuritis* have also been recognized. Often, the cause of the copper deficiency is unclear. Spinal cord magnetic resonance imaging (MRI) in patients with copper deficiency myelopathy may show an increased T2 signal, most commonly in the dorsal midline cervical and thoracic cord. The clinical and imaging picture is very similar to the subacute combined degeneration seen in patients with vitamin B<sub>12</sub> deficiency. These imaging findings may be reversible with normalization of serum copper.

**Folate** Folate is necessary for the production and maintenance of new cells. This is especially important during periods of rapid cell division and growth such as infancy and pregnancy. Folate is needed to replicate DNA. It also helps prevent changes to DNA that may lead to cancer. Folic acid is very important for all women who may become pregnant. Adequate folate intake during the periconceptual period helps protect against a number of congenital malformations including neural tube defects. *Neural tube defects* result in malformations of the spine (spina bifida), skull, and brain (anencephaly).

The risk of neural tube defects is significantly reduced when supplemental folic acid is consumed in addition to a healthy diet prior to and during the first month following conception. Women who could become pregnant are advised to eat foods fortified

with folic acid or take supplements in addition to eating folate-rich foods to reduce the risk of some serious birth defects. Taking 400 mcg of synthetic folic acid daily from fortified foods and/or supplements has been suggested and this could potentially reduce the risk of neural tube defects as much as 48%. The Recommended Dietary Allowance (RDA) for folate equivalents for pregnant women is 600 mcg.

**Cerebral folate deficiency** can be defined as a neuropsychiatric condition associated with low levels of 5-methyltetrahydrofolate (5MTHF), the active folate metabolite in the cerebrospinal fluid, in association with normal folate metabolism outside the central nervous system, as reflected by normal hematological values, normal serum homocysteine levels, and normal levels of folate in serum and erythrocytes. Infantile-onset cerebral folate deficiency is a neurologic syndrome that develops four to six months after birth. Its major manifestations are marked irritability, slow head growth, psychomotor retardation, cerebellar ataxia, pyramidal tract signs in the legs, dyskinesias (e.g., choreoathetosis and ballismus), and, in some cases, seizures and autism. After the age of 3 years, central visual disturbances can become manifest and lead to optic atrophy and blindness. Early detection and diagnosis of cerebral folate deficiency are important because folinic acid at a pharmacological dose and the 5MTHF derivative can bypass autoantibody-blocked folate receptors and enter the cerebrospinal fluid by way of the reduced folate carrier. This route restores the folate level within the central nervous system and can ameliorate the neuropsychiatric disorder.

In addition, considerable evidence now supports the concept that folate plays a key role in determining the levels of homocysteine. Low concentrations of folate may increase levels of *homocysteine*, which, as it was explained previously, is an independent risk factor for heart disease and *stroke*. High blood levels of homocysteine have also been linked with the risk of dementia and Alzheimer's disease. There is therefore interest in whether dietary supplements of folic acid can improve cognitive function of people at risk of cognitive decline associated with ageing or *dementia*, whether by affect-

ing homocysteine metabolism or through other mechanisms.

**Vitamin A** Retinol, the dietary form of vitamin A, is a fat-soluble, antioxidant vitamin important in vision and bone growth. Vitamin A is required in the production of rhodopsin, the visual pigment used in low-light levels. Vitamin A deficiency is common in developing countries but rarely seen in developed countries.

Approximately 250,000 to 500,000 malnourished children in the developing world go blind each year from a deficiency of vitamin A. *Night blindness* is one of the first signs of vitamin A deficiency. Vitamin A deficiency contributes to blindness by making the cornea very dry and damaging the retina and cornea—*keratomalacia*. Treatment of vitamin A deficiency can be undertaken with both oral and injectable forms.

**Vitamin E** Vitamin E deficiency in clinical practice is uncommon except in disorders with impaired absorption of fat-soluble vitamins. The resulting deficiencies deplete vitamin E in nervous system and results in a progressive *spinocerebellar degeneration* and demyelinating *neuropathy*. The full symptomatic deficiency state is associated with ataxia, hyporeflexia, ophthalmoplegia, myopathy, retinal degeneration, and a sensory-motor polyneuropathy. It may be mistaken for a variety of other syndromes including multiple sclerosis and Friedreich ataxia. Patients with severe, prolonged deficiency may develop complete blindness, *dementia*, and cardiac arrhythmias. There are also adult forms of spinocerebellar degeneration that may be associated with abnormalities of the alfa-tocopherol transfer protein. Treatment must be tailored to the underlying cause of vitamin E deficiency and may include oral or parenteral vitamin supplementation. The more advanced the deficits, the more limited the response to therapy.

**Interaction of Malnutrition with Other Neurologic Diseases** Nutritional deficiencies often come to pass unnoticed in the context of patients with neurologic diseases of diverse etiology. This lack of detection and early correction can modify drastically the evolution of a patient and the response to a suitable treatment. As an

example, the impairment in nutritional status, consequent to quantitative and qualitative inadequacy of diet, could be one of the first steps in the development of co-morbidities in disabled subjects.

Regarding *cerebrovascular disease*, previous studies have suggested that undernourished patients with acute stroke do badly. There is a nutritional deterioration during hospitalization which may be attributed to factors other than inadequate number of calories administered. Malnourished patients had a higher stress reaction; therefore, patients with acute stroke must be considered moderately hypercatabolic but with low caloric requirements. Catabolic disease alters body composition rapidly, with a gradual shrinkage of body fat and body cell mass compartments. The neuroendocrine response to injury modifies the metabolism of carbohydrates, inducing mobilization of fat stores and consequently a decrease in triceps skinfold (TSF).

Nearly every aspect of the immune system is damaged by inadequate nutrition and stress reaction. Immunosuppression may worsen the prognosis in poststroke recovery, with an increased susceptibility to infections and bedsores, which occurred in our patients. Undernourished patients are more likely to develop pneumonia, other infections, and gastrointestinal bleeding during their hospital admission than other patients. This is reliable evidence that malnutrition early after stroke is independently associated with increase mortality and a poor long-term outcome.

The treatment of the epilepsies has demonstrated that some medications influence negatively the serum levels of some essential micronutrients with its clinical secondary effects. There is emerging evidence to support the unfavorable effects of some antiepileptic drugs on the plasma homocysteine concentrations. Elevated homocysteine levels induced by anti-epileptic drug administration can theoretically increase not only the risk of vascular occlusive diseases, but also the risk of resistance to anti-epileptics and development of refractory epilepsy. The underlying mechanism for homocysteine increase seems to be a decrease of cofactor molecules in patients using carbamazepine

## KEY POINTS

- Approximately 250,000 to 500,000 malnourished children in the developing world go blind each year from a deficiency of vitamin A.
- Vitamin E deficiency in clinical practice is uncommon except in disorders with impaired absorption of fat-soluble vitamins. The resulting deficiencies deplete vitamin E in the nervous system and results in a progressive spinocerebellar degeneration and demyelinating neuropathy.
- Malnutrition early after stroke is independently associated with increase mortality and a poor long-term outcome.
- Elevated homocysteine levels induced by antiepileptic drug administration can theoretically increase not only the risk of vascular occlusive diseases, but also the risk of resistance to antiepileptics and development of refractory epilepsy.

and phenytoin (pyridoxal 5'-phosphate and folic acid, respectively). The administration of a combined treatment with folic acid could ameliorate these difficulties. Also, epilepsy patients taking oxcarbazepine (OXC) or carbamazepine (CBZ) have significantly lower 25-OHD (25-hydroxyvitamin D) than do normal controls, with a pattern of changes in other bone biomarkers suggestive of secondary hyperparathyroidism. It is prudent for patients taking CBZ or OXC to be prescribed vitamin D replacement.

### PREVENTION

Developing countries must work to ensure that development policies and projects are

designed to include nutrition improvement objectives. Furthermore, in the low-income food-deficit countries, where most of the world's malnourished people live, economic growth and poverty alleviation must be based on better development of agricultural resources and improvement of food supplies. Meeting the MDG targets of achieving the goal of halving global hunger is urgent, and the question that needs to be addressed is not whether the international community can achieve this goal in time but whether it can afford not to.

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HIV infection has become increasingly prevalent globally, with more than 40 million infected individuals worldwide. There are nutritional and metabolic issues that significantly impact morbidity and mortality in HIV-infected populations. In addition, malnutrition has been associated with an increased risk of transmission of HIV from infected mothers to infants, and malnutrition may further compromise HIV-infected individuals who have tuberculosis or persistent diarrheal disease.



# MALNUTRITION AND BRAIN DEVELOPMENT: A REVIEW

Kenton R. Holden

Malnutrition is real, is a worldwide health problem, exists in many forms, affects the developing and mature nervous system, and has acute and chronic health implications. Although these problems and concerns are well known, most studies on the effects of malnutrition on neurodevelopment and function have been in experimental animals. While these studies were essential to establish casual relationships, attempts to interpret and extrapolate toward human relevance commonly become clouded by hype and misconceptions. Only recently have researchers begun looking at the one-third or more of the world's children with various degrees of malnutrition and how that may acutely or chronically limit their intelligence or psychomotor development and function.

The brain does not develop uniformly during fetal and neonatal life. It has characteristic, well-defined stages of growth both anatomically and biochemically that result in critical periods of localized growth and development. The development of any part of the brain occurs in stages: induction of neural plate, localized proliferation of cells in different regions, migration of cells, formation of parts by cell aggregation, differentiation of immature neurons, formation of connections, selective cell death, and modifications of remaining connections. Most of these changes occur caudally to rostrally.

Structural changes result in an increase in brain size and weight with the greatest growth in size occurring before the greatest gain in weight. Not all regions of the brain grow at the same rate. Over 70% of the total number of brain cells that will last a lifetime are formed in the first 8 weeks postconception. Over 60% of the energy that the fetus derives from the placenta is used for normal neurogenesis. All of the actively changing

regions of brain growth are highly susceptible to insult. Human neurogenesis peaks at 14 weeks gestation and is relatively complete by 25 weeks gestation when the approximate number of adult neurons is present. Known exceptions are some of the neurons of the hippocampus and cerebellum.

Gliogenesis usually produces glial cells following neuron production in any region of the brain. The production of glial cells continues throughout adult life and is primarily a postnatal event. However, early gliogenesis has begun by the 16th week of gestation in humans. Despite the heterogeneity of the cell population, the arrangement of neurons must be completed satisfactorily for normal functioning to result. Synaptogenesis is the contact between axons and target cells that starts before neurogenesis is completed through the growth of axons and dendrites (neurites). After an excess of neurites and neurons form, programmed cell death and synapse reorganization follow (one or more times) as the final stages of brain morphogenesis. Each brain region has a specific timed series of events for these maturation processes.

The discovery in mammals that a narrow window of vulnerability exists where malnutrition-induced brain damage may be responsible for limiting neurodevelopment potential is recent knowledge. Anatomical studies of specific animal brain areas have confirmed this grossly and microscopically to include even cell architecture and synaptic zones. Although there was originally thought to be a large irreversible component to the effects of malnutrition, recent information has shown that the brain can make remarkable recovery from early malnutrition. Persistent abnormalities that remain include a reduced number of cortical dendrites in

## KEY POINTS

- Malnutrition is a worldwide health problem which has acute and chronic health implications on developing and maturing nervous systems.
- The brain has characteristic well-defined stages of localized growth and development, with many areas not growing at the same rate.
- Over 70% of the total number of brain cells that will last a lifetime are formed in the first 8 weeks postconception. Human neurogenesis peaks at 14 weeks of gestation and is relatively complete by 25 weeks gestation.
- Although gliogenesis begins at 16 weeks gestation, production continues throughout adult life and is primarily a postnatal event.
- Recent studies indicate that only a narrow window of vulnerability exists where malnutrition-induced brain damage may be responsible for limiting neurodevelopment progress.
- Recent information has shown that the brain can largely recover from an early malnutrition insult.

**KEY POINTS**

- Although short apical dendrites, fewer spines, and dendritic spine abnormalities occur in human infant malnutrition, altered neurotransmitter function and responsiveness may play a larger role in adverse outcomes.
- The mechanism remains unclear from animal studies as to how the adverse effects of malnutrition on the hippocampus specifically affect brain function.
- The cerebellum may be the CNS structure most vulnerable to malnutrition, but these abnormalities appear reversible with nutritional rehabilitation. It remains unclear why more sensitive tests of psychomotor coordination demonstrate subtle long-term motor abnormalities.
- Developmental disorders of the CNS in the initial half of gestation primarily affect cytogenesis and histogenesis. In the latter half of gestation and in the postnatal period, brain growth and differentiation are primarily affected.
- “Nature versus nurture” no longer appear separate entities from one another, but more than ever appear reciprocal through interactions of the genetic code with the relevant environment.

synaptic spines, a reduction in brain myelin, and increased cortical neuronal mitochondria. In humans, short apical dendrites, fewer spines, and dendritic spine abnormalities occur in severe infant malnutrition. Neurotransmitter alterations appear to persist after nutritional recovery as reflected by diminished sensitivity of cortical structures to basal electrophysiological stimulation. This possibly reflects altered neurotransmitter function at the receptors and/or a decrease in number of receptors. Further studies have shown a decreased ability of adrenergic receptors to exhibit downregulation, although normal upregulation of beta-adrenergic receptors occurs in rat studies. Can malnutrition make the brain less able to adapt to stressful situations? The depressed brain reaction to noradrenergic, serotonergic, and GABAergic drugs is not a generalized decrease in responsiveness to all drugs since caffeine and amphetamines elicit normal behavioral responses.

Although neuroanatomical studies in rats have supported for years the adverse effect of malnutrition on the hippocampus, recent information appears to refute this finding at the cellular and neurotransmitter levels. Cell size, number, and dendritic branching in the hippocampus are reduced by early malnutrition as they are in other brain regions, and appear not to be reversed with nutritional rehabilitation. The number of synapses per neuron, however, which is initially less than in control rats who were not malnourished, eventually ends up at 250 days of nutritional rehabilitation with one-third more synapses per neuron than the well-fed controls. Electrophysiological data do not help clarify the question of permanent hippocampal dysfunction. It is clear that the firing pattern of hippocampal neurons is altered by malnutrition, but unclear how this specifically affects brain function.

The cerebellum may be the most vulnerable of central nervous system structures to early malnutrition. Gross abnormalities in electrophysiological activity of Purkinje cells and suppression of the synapse: neuron ratio is well documented in animal studies. Some abnormalities appear nonreversible, such as the reduced ratio of granule: Purkinje cells, but the functional significance

of these findings is not clear. However, some of the alterations appear to be reversible with nutritional rehabilitation. Standard batteries of psychomotor tests generally fail to reveal long-term effects of malnutrition in either animals or humans, but more sensitive tests of psychomotor coordination demonstrate subtle motor differences. It is easy to postulate that changes secondary to undernutrition may affect evoked neurotransmitter release and/or receptor sensitivity which would lead to changes in behavior and function. However, definitive data on the influence of nutrition on this and other areas of human neurologic development are hard to find.

There are two general classes of central nervous system (CNS) developmental disorders. The first occurs during the initial half of gestation and affects cytogenesis and histogenesis. The second occurs during the second half of gestation and early postnatal period and affects brain growth and differentiation. These latter occurrences include both progressive events (neuronal maturation, connection formation, and synaptogenesis) and regressive events (cell death and selective elimination of processes). Both events critically shape the maturation of brain circuitry. Human behavior emerges from this process through cells and intercellular connections which are estimated at 100 billion cells, each with up to 10,000 connections. It remains to be shown what minimal amount of specific nutrient or what degree of global malnutrition is necessary to produce long-term alterations on these cells and connections which have a non-reversible change. It also remains unclear what the exact role of epigenetics and the non-food environment has on each one of these variables, as well as on the regulatory mechanisms and genes. “Nature versus nurture” no longer appear separate entities from one another, but more than ever appear reciprocal in shaping each individual through interactions of the genetic code with the relevant environment.

The image of malnutrition is large eyes, lined face with taut skin, and bony rib cage, but this represents only 1% to 2% of all malnutrition. The majority of protein-energy malnutrition (PEM) of the world is represent-

**TABLE 2.1** Protein-Energy Malnutrition (PEM)**Symptoms**

Irritability  
 Apathy  
 Decreased social interactions  
 Attention deficits  
 Anxiety  
 Drowsiness  
 Recurrent infections

**Physical Finding (Signs)**

Poor weight gain  
 Decreased linear growth  
 Decreased head circumference  
 Decreased subcutaneous tissue  
 Edema  
 Oral changes—stomatitis  
 Abdominal distention—ascites  
 Skin—rash, cheilitis  
 Hair/nails—brittle, alopecia

ed by the underweight 2 year old, the stunted 4 year old with recurrent infections, or the glazed-over eyes of a 7 year old behind a school desk (Table 2.1). Over one-third of the world's children are subject to this risk. The World Health Organization (WHO) estimates that 350 million children are malnourished based on stunted height or low weight to age. Data on timing of growth faltering taken from the WHO Global Database on Child Growth and Malnutrition, which includes data from recent surveys in 39 developing countries in Latin America, Asia, and Africa, has been calculated and compared to data from the United States and Britain. Using functional classifications for child malnutrition to separate acute malnutrition from chronic malnutrition, acutely malnourished children had adequate height for age but inadequate weight for height ("wasted"), and chronically malnourished children had inadequate height for age ("stunted"). Chronically malnourished children could also be acutely malnourished, which would mean they were both stunted and wasted. Stunted children usually are not in immediate danger of dying, whereas

wasted children more likely need urgent attention to prevent death by starvation.

The WHO data indicate that mean weights in malnourished children begin faltering at 3 months of age, rapidly decline until 12 months, and decrease further by 18 months. They then resume "catch-up" after 18 to 24 months. Weight for height falls off over the first 15 months of life, then improves. The length/height data at birth are remarkably close to the mean for the United States and Britain, but faltering starts immediately and lasts for 3 years. How common is growth stunting? Stunting affects 182 million (33%) and wasting affects 150 million (27%) of the world's children. More than half the children in southern Asia and a third of those in sub-Saharan Africa and Latin America are growing up stunted. Most of this stunting is attributed to PEM (Table 2.2). The infants born to stunted female adolescents are at risk for high rates of prematurity. In this and other examples the effects of nurture on the brain cross generations and act like "inherited" traits of nature. This manuscript will not cover the nutritional deficiencies associated with chronic medical conditions such as cystic fibrosis, chronic renal failure, malignancies, congenital heart disease, neuromuscular diseases, or multiple food allergies.

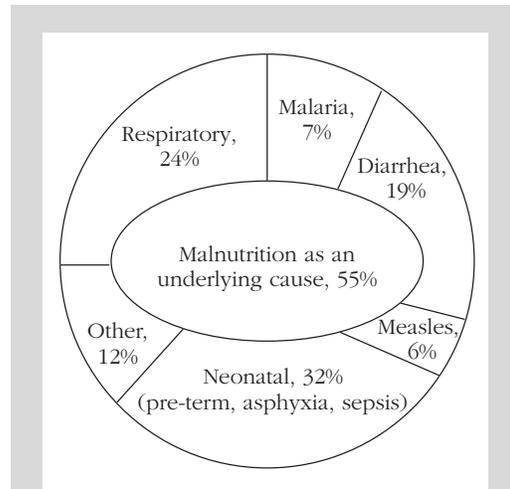
About 55% of the 13 million deaths under age 5 years in the world each year, primarily from developing countries, are in malnourished children (Figure 2.1). Of those 7 million nutrition-involved deaths, 80% are mildly to moderately malnourished. Feeding programs have not solved this problem. Different approaches including parent and community involvement to improve public health, water, immunizations, improved child care, and education need to be supported along with the teaching of agricultural skills to address this issue. Women of child-bearing age would appear to be an appropriate select population to address specific nutritional needs. Confronting the negative attitude towards women in societies where their worth may be perceived as being low may be as important as poverty in playing a role in this massive worldwide epidemic of malnutrition and its effect on the developing nervous system.

**KEY POINTS**

- The WHO estimates that 350 million children are malnourished based on low weight or stunted height for age. Appropriate breast-feeding could significantly reduce this figure.
- Functional classifications for childhood malnutrition include "wasted" for acute malnutrition and "stunted" for chronic malnutrition. Acute malnutrition reveals adequate height for age but inadequate weight for height (wasted). Chronic malnutrition has inadequate height for age (stunted).
- Chronically malnourished children can also be acutely malnourished, which means they are both stunted and wasted. Stunting usually implies there is no immediate danger of dying, whereas wasted children usually need urgent attention to prevent death from starvation.
- More than half the children in southern Asia and a third of those in sub-Saharan Africa and Latin America are growing up stunted. Most stunting is attributed to protein-energy malnutrition (PEM).
- Of the 13 million deaths under 5 years old in the world each year, about 55% are in malnourished children. Of those, 80% are in mildly to moderately malnourished children.

**KEY POINTS**

- Feeding programs have not solved the problem. Improving the status of women in societies where their worth may be perceived as low may be as important as relieving poverty in correcting the epidemic of malnutrition.
- In developing countries gain in life expectancy as well as reduction in child and infant mortality has been striking over the last 50 years.
- Of the 5 million neonatal (first 28 days of life) deaths which occur worldwide yearly, 98% are in developing countries. Low birth weight and prematurity are significant factors, but infections contribute to the majority of deaths.
- In general, with regard to prognoses for neonates in developing countries, what is good healthwise for the mother is good for the unborn or newly born child.
- Kwashiorkor is PEM with the presence of edema (decreased protein with low normal caloric intake), and marasmus is PEM with absence of edema (decreased protein and caloric intake).



**FIGURE 2.1** Of the 13 million children under five who die each year, primarily from developing countries, over 7.1 million succumb to malnutrition as an underlying cause. (2005)

Life expectancy in developing countries rose from 40 to 64 years between 1950 and 1998. The reduction in child mortality for children <5 years old fell from 193 to 86/1000 live births between 1960 and 1998. Infant mortality declined from 124 to 59/1000 live births during the same time. Neonatal mortality (first 28 days of life) now accounts for the majority of all infant (first 12 months of life) deaths. Of the 5 million neonates who die each year, 98% are from

developing countries. Low birth weight is a significant factor in perinatal and neonatal mortality. Most births and deaths in developing countries occur at home, are not attended by a doctor or allied health worker, are underreported; information on the cause of death is usually incomplete. Infection (42%), asphyxia/birth trauma (32%), and congenital anomalies (11%) are the most common documented etiologies on death certificates with prematurity listed as only 10%. Prematurity is associated with half the deaths within the first 24 hours of life, but in the first week of life, infection (45%) and prematurity (21%) are listed as the major causes of death. Later neonatal deaths (7 to 28 days) are primarily attributable to infection (82%). With few exceptions with regard to prognosis for neonates in developing countries, what is good healthwise for the mother is good for the unborn child.

**PROTEIN-ENERGY MALNUTRITION**

WHO defines malnutrition as “the cellular imbalance between supply of nutrients and energy and the body’s demand for them to ensure growth, maintenance, and specific functions.” *Kwashiorkor* is PEM with the presence of edema (decreased protein with low normal caloric intake). *Marasmus* is PEM with the absence of edema (decreased protein and caloric intake). In PEM endemic areas, supplementary feeding that meets nutritional requirements of children during the first 18 to 24 months of life may help pre-

**TABLE 2.2** Failure to thrive evaluation

**Evaluation**

Height-for-age or weight-for-height >2 standard deviations below mean for age, or less than 90%–95% of expected value with relatively spared head circumference (microcephaly possible)  
 Less than 5 cm/year of growth in children >2 years old  
 Body mass index (BMI)

**Laboratory Tests**

Complete blood count, blood smear, blood urea nitrogen/creatinine, blood lead, albumin/prealbumin, total protein, liver function, cholesterol, glucose, thyroid function, calcium, electrolytes, HIV titer, urinalysis, stool for ova and parasites  
 Skin test for tuberculosis and/or chest x-ray  
 5-day diet log

vent part of the cognitive delays caused by extreme poverty and malnutrition. The longer the duration of the intervention and the greater the breadth of the intervention (nutrition, health, education), the higher the probability of recovery. This appears to be true in spite of the evidence of permanent cortical injury with PEM represented by neuropathological findings of decreased brain density, decreased arborizations of dendrites, decreased width of cortical cells, and permanently altered neurotransmitter systems.

When PEM is prevalent, micronutrient deficiencies in children and expectant mothers are also likely to be present and can have a detrimental effect on growth and development both before and after birth (Case 1). The most common micronutrient deficiencies reported in children and women of childbearing age are iron, iodine, folate, vitamin D, and vitamin A (Table 2.3). In a recent study of dietary intakes of women of

childbearing age in Honduras, iron intake was 77% of the United States recommended dietary allowance per day (RDA), iodine was 21% RDA, folate was normal RDA prior to the new recommendations, and vitamin A was 65% RDA, and vitamin D was not reported. Other numbers of interest included a protein intake equal to normal RDA, caloric intake of 67% RDA, both essential fatty acids (EFA) were 23% and 30% RDA, copper, zinc, B<sub>6</sub> and B<sub>12</sub> were 70% or less of the RDA.

Studies of PEM and child development have been too compartmentalized with only specific aspects assessed, ignoring other variables that also affect development. Physical growth, motor development, motor activity, and emotional regulation are not independent of each other. Children dealing with social and physical issues do not depend on cognition alone. They need the ability to inhibit inappropriate behavior and cope with inter-

#### KEY POINTS

- Where PEM is prevalent, micronutrient deficiencies in children and women of childbearing age are likely. The most common micronutrient deficiencies are iron, iodine, folate, vitamin D, and vitamin A.
- When assessing malnutrition and its effect on child neurodevelopment, remember to consider multiple variables.

#### CASE 1

A 4-year-old Hispanic girl from rural Honduras with normal developmental status develops persistent irritability over a 1 month period. In addition, she developed anorexia, lassitude, insomnia, persistent nonbloody diarrhea, and a rash in light-exposed areas. Her parents report she has decreased stamina, appears “weak,” “wobbly,” and falls more frequently. There have been no serious accidents, illnesses, fever, or exposure to toxins. A recent change in dietary habits includes a fondness for corn tortillas and very little meat intake in a “picky” eater.

On examination, her height and head circumference are at the 10th percentile, and weight is at the 3rd percentile. She is irritable throughout the exam. Scaly erythematous skin lesions are present on the forehead, neck, hands, and arms. The remainder of the general exam is normal. Cranial nerves are intact with mild disc pallor bilaterally. Mild generalized muscle weakness with normal tone is present. A mild tremor when reaching for objects and an unsteady gait are observed. Deep tendon reflexes are 3 to 4+ in the limbs with plantar extensor responses bilaterally.

Pellagra presents as a multisystem disease, so a high index of suspicion helps contribute to the proper diagnosis. This condition is endemic to areas where corn forms the staple food, and where meat intake is low. Response to treatment of a high protein diet and vitamin supplements is usually prompt and supports the clinical diagnosis. Poor sleeping and restlessness may be the result of neuropathic burning pain. If neurologic involvement is mild, complete recovery commonly takes place.

**Comment:** In more severe cases, histological examination of the brain shows degeneration of the Betz cells of the motor cortex, and to a lesser extent, of the cerebellar Purkinje cells. In the spinal cord, there is degeneration of myelin and axons of the posterior columns, pyramidal, and spinocerebellar tracts. Demyelination of the peripheral nerves is common. Although children are affected more frequently than adults, manifestations are usually milder than in adults. However, infants and young children with pellagra of longer duration are at high risk for permanent sequelae including psychomotor retardation, gait and coordination abnormalities, and psychological aberrations.

**KEY POINTS**

- Hunger and/or food insecurity may constitute even additional risk factors rarely considered as variables in the evaluation of malnutrition.
- Some of the strongest data to date supporting the role of the social environment in moderating the effects of an early nutritional insult come from the Dutch famine of 1944 to 1945.
- Immune response alterations early in the course of malnutrition mimic those seen in acquired immune deficiency syndrome.
- Animal studies show significant, and often permanent, alterations in the anatomy, physiology, and neurochemistry of the hippocampus in response to gestational PEM.

**TABLE 2.3** Micronutrient Deficiencies

Micronutrients	Deficiency Signs and Symptoms
Iron	Fatigue, inattention, decreased cognition, headache, glossitis, thin nails, anemia
Iodine	Goiter, neurodevelopmental delays, mental retardation
Folate	Glossitis, anemia, neural tube defects
Vitamin D	Poor growth, rickets, hypocalcemia
Vitamin A	Night blindness, xerophthalmia, poor growth, hair changes

nal or external stimuli. All of these functions influence behavioral-emotional adjustments and the ability to function in different environments. Children from developing countries with chronic undernutrition have associated increased anxiety, attention deficits, increased school absence and tardiness, lower levels of social responsiveness, and decreased affect. Studies have consistently shown that poverty is one the most powerful predictors of psychiatric and functional problems in children. In addition to lack of basic needs and adult malnutrition, there is higher marital discord, single parenthood, family dysfunction, family and neighborhood violence, and parental psychopathology when compared to more advantaged families.

“Hunger” may constitute even another variable risk factor/burden. Multiple stressors probably put these children at a significantly greater risk for development of psychosocial problems. Yet maternal PEM appears not to produce permanent neurologic or intellectual deficit in the fetus in some studies since brain growth appears unaffected as reported with fetal exposure to PEM during the Dutch famine in 1944 to 1945. Mental performance at age 19 years of children conceived during the Dutch famine appeared uninfluenced by this early nutritional insult. Research over about three decades on the functional consequences of PEM has shown that the social environment apparently moderates the effects of an early nutritional insult.

In addition to impairment of physical growth, cognitive and behavioral abilities, and other physiological functions, immune response changes occur early in the course of malnutrition in a child. Loss of delayed

hypersensitivity, fewer T lymphocytes, impaired lymphocyte response, impaired phagocytosis secondary to decreased complement and certain cytokines, and decreased secretory immunoglobulin A (IgA) are some changes that may occur. These changes mimic those seen in acquired immune deficiency syndrome (AIDS).

Studies on PEM and the effects of prenatal protein malnutrition and neonatal stress on central nervous system (CNS) responsiveness in rats have looked at the hypothalamus and the hippocampus. These are important CNS areas that are felt to be vulnerable to such manipulations. It is currently thought that anatomical maturation of brain regions of the CNS and consequent psychomotor development depend on (1) heredity/genetic directives, (2) environmental influences, and (3) an “adequate” diet. Gestational protein deprivation results in significant, and often permanent, alterations to the anatomy, physiology, and neurochemistry of the hippocampal formation. Findings of higher granule cell inhibition in response to electrophysiological challenge also suggest an alteration in hippocampal plasticity with gestational malnutrition. The hippocampal formation in rats is also affected by neonatal isolation stress. This stress alters hippocampal neuroplasticity in such a way that its effect endures into adulthood. One could postulate that a combination of these effects could be additive. In particular, the hypothalamic-pituitary-adrenal stress response and the serotonergic functioning in the hypothalamus and hippocampus may be synergistic to the detriment of final neurodevelopmental outcome.

## PROTEINS AND CARBOHYDRATES

The effect of protein and carbohydrates (macronutrients) on brain and behavioral development is well documented and has been discussed at length previously in this chapter under PEM, although causation for specific diseases has not been well established in children. An additional point of interest is that several amino acids act as precursors for neurotransmitters, such as: tryptophan goes to 5-hydroxytryptamine (serotonin), and tyrosine goes to dopamine, nor-epinephrine, and epinephrine. Serotonin has been shown to have both inhibitory and stimulatory effects on neurite outgrowth, glial proliferation, and synaptogenesis. Serotonin activates autoreceptors on neurons (serotonin neurons) as well as postsynaptic-like receptors on glial and neuronal targets. Serotonin appears to be an important developmental signal during brain development and possibly a modulator of cell proliferation within the neuroepithelium. Serotonin is felt to be related to ancillary modulation processes, such as sensory and motor processes and motivation. Spatial memory deficits result from combined alterations in both serotonin and cholinergic systems.

A high carbohydrate diet increases brain tryptophan and serotonin and reduces tyrosine; thus, modulation of one neurotransmitter by diet can affect other neurotransmitters, which in turn might alter behavioral responses to a stressful event. Numerous other neurotransmitters have amino acid bases such as gamma-aminobutyric acid (GABA), glutamate, and glycine. Much less is known of dietary effects on these neurotransmitters, especially since some of them are capable of being synthesized in the brain. The central importance of the N-methyl-D-aspartate (NMDA) glutamate receptor for learning is strongly supported by the behavioral literature. Further studies are needed to clarify the role of nutritional deficiencies on this area of brain function.

## FATS INCLUDING ESSENTIAL FATTY ACIDS

If adipose tissue is excluded, the brain is the most lipid-concentrated organ in the body. About 10% of the brain weight is lipid. About 50% of the dry weight is lipid. Of this

lipid, about 50% is phospholipid, 20% cholesterol, and 15% to 20% cerebrosides. There are small amounts of sulfatides and gangliosides. During the last trimester of human intrauterine growth, estimates for utilization in de novo synthesis of tissues are approximately 522 mg/day of n-6 EFA and 67 mg/day of n-3 EFA. This does not take into account the amount of fatty acids oxidized to meet any energy requirements for tissue accretion. Approximately 2783 mg of n-6 EFA and 387 mg of n-3 EFA accrue in adipose tissue each week in utero. This is a large draw on maternal stores, and any limitation in size of maternal fatty acids stores has critical consequences on fetal growth and development.

The rapid synthesis of structural brain lipids in the third trimester causes increases in cell size, cell type, and cell number. Adequate amounts of EFA linoleic and alpha-linolenic acid are needed from dietary sources as precursors of arachidonic acid (ARA) and docosahexaenoic acid (DHA). Although levels of linoleic acid (LA, 18:2n-6) and alpha-linolenic (LNA, 18:3n-3) EFA are consistently low (<1% of brain and retina fatty acids) in the brain during the last trimester of pregnancy, accretion of long-chain EFA desaturation products 20:4n-6 (ARA) and 22:6n-3 (DHA), especially the DHA, is greater in the prenatal period than the postnatal period. The long-chain polyunsaturated fatty acids (PUFA) ARA and DHA are major constituents of the human central nervous system and are functionally important components of membrane phospholipids. PUFA can not be synthesized de novo from 2-carbon fragments by mammalian tissue, nor do biochemical pathways exist for the interconversion of their n-6 and n-3 forms. It is apparently critical that the developing fetus obtain at the correct time the correct balance of n-6 and n-3 PUFA to ensure proper and complete development of the CNS. Brain processes likely dependent on these amounts and ratios being within normal limits include apoptosis, gene transcription, neurite outgrowth, membrane excitability, prostaglandin formation, desaturation-elongation, membrane fluidity and elasticity, inflammatory and immunological events, and cerebral ischemia.

## KEY POINTS

- Several amino acids act as precursors for neurotransmitters, some of which (e.g., serotonin) appear to be signals during brain development as well as modulators of cell proliferation.
- The brain is the most lipid-concentrated organ in the body. The rapid synthesis of structural lipids for gestational brain growth requires adequate intake of essential fatty acids (EFA).
- It appears critical to the developing fetal brain that the correct balance of n-6 and n-3 PUFA be supplied at the correct time to ensure normal development and maturation.

## KEY POINTS

- The third trimester of gestation is primarily when the developing neural tissue is experiencing maximum cellular differentiation and active synaptogenesis. Genetic and dietary factors both play a role.
- EFA are structural components of all tissues and are indispensable for cell membrane synthesis.
- Regulation of gene expression by long-chain PUFA during CNS development occurs at the transcriptional level and is mediated by nuclear transcription factors activated by fatty acids.
- PGE, a product of ARA, are important contributors to regulatory functions in the brain and can influence neural activity by modulating neurohormones and neurotransmitters.

Timing of early brain developmental events and functional milestones generally appear to be secondary to an initial transient organization of connections after the layering out stage of cortical structures and brain nuclei. This is followed mostly postnatally by structural and molecular reorganization. This remodeling is a hallmark of typical primate cortical development which occurs preterm, neonatally, in early childhood, prepuberty, and postpuberty. In the third trimester the developing neural tissue is experiencing cellular differentiation and active synaptogenesis. While in utero, the fetus relies on the mother for its supply of many of the fatty acids, particularly EFA. It is now apparent that different fatty acid diet studies alter neuronal and glial cell composition differently in a region and time-specific manner. This is in addition to genetic factors which might also be relevant.

The action of n-6 and n-3 fatty acids on metabolic and physiological pathways likely involves three general mechanisms: (1) membrane phospholipid fatty acids influence the microenvironment of membrane bilayers, and in turn affect activity of membrane-associated proteins, receptors, transport systems, and ion channels; (2) membrane phospholipids and their n-6 and n-3 fatty acids function as signal molecules and as precursors of eicosanoids; and (3) n-6 and n-3 have direct effects on gene expression through peroxisome proliferator activated receptor (PPAR)-dependent and PPAR-independent mechanisms.

EFA are structural components of all tissues and are indispensable for cell membrane synthesis. The brain, retina, and other neural tissues are rich in long-chain PUFA. The essential nature of n-6 EFA and n-3 EFA in early life of human and animal studies for growth and cognitive development is well established. Their largest role relates to neural development and maturation of sensory systems. Even preterm infants are able to form ARA and DHA from EFA. Regulation of gene expression by long-chain PUFA during retinal and CNS development occurs at the transcriptional level and is mediated by nuclear transcription factors activated by fatty acids. These nuclear receptors are part of the steroid hormone receptor family. Two

types of PUFA responsive transcription factors have been characterized: PPAR and the hepatic nuclear factor 4 alpha. Human maternal plasma and red blood cell phospholipid 22:6n-3 concentrations start to increase in very early pregnancy (0 to 10 weeks) which can not be explained by changes in dietary intake alone. This is probably another unexplained early maternal adaptation to the needs of a developing fetus.

Membranes that are specialized for rapid transmission of light (outer segments of the retina rods and cones) contain 90% to 95% of their lipid as phospholipid (phosphatidylethanolamine, phosphatidylserine, phosphatidylcholine). ARA may function as a retrograde transmitter involved in synaptic plasticity. ARA is also a precursor of the eicosanoids (prostaglandin, thromboxanes, leukotrienes) on which normal brain function depends. Prostaglandins (PGE) are important contributors to regulatory functions in the brain and can influence neural activity by modulating neurohormones and neurotransmitters. PGE<sub>2</sub> inhibits the release of norepinephrine and dopamine and may augment the release of serotonin.

In rat and piglet brains, chronic deficiency of omega-3 fatty acids alters dopamine and serotonergic neurotransmission by reducing dopamine receptor binding and increasing serotonin receptor density in the frontal cortex. This is of increased interest because of dopamine's role in cognition, modulation of attention and motivation, and visual function in early childhood. In addition, the earliest events in G-protein-coupled signaling (receptor conformation change, receptor-G-protein binding, and phosphodiesterase activity) are reduced in membranes lacking n-3 polyunsaturated acyl chains. Efficient and rapid propagation of G-protein-coupled signaling requires polyunsaturated n-3 phospholipid acyl chains. Administration of a diet deficient in EFA during development causes hypomyelination in the rat brain. Also shown in rats is that lipids can play a role in accelerating myelinogenesis. Accelerated myelinogenesis is related to a precocious appearance of behavioral reflexes. DHA depletion from developing retina and brain leads to abnormalities in the

electroretinogram, visual evoked potential responses, and possibly learning (cognitive) behaviors. The strongest evidence for beneficial effects of long-chain PUFA supplementation with DHA and ARA comes from measures of visual development. ARA is essential for normal growth, cell signaling, and as a precursor to series 2 eicosanoids and series 3 leukotrienes (which also play a role in synaptic transmission).

Experiences in low-birth-weight infants (LBWI) support that differences in cognitive function and growth may be due to the amount of weight gain during pregnancy, the act of breast-feeding, motivation, and the education level of the mother rather than the chemical composition of human milk. The debate still continues over adding ARA or DHA to diets of LBWI. Term babies are able to synthesize both ARA and DHA in sufficient amounts for normal brain development, provided their diets contain adequate portions of essential 18-carbon fatty acid precursors.

## MICRONUTRIENTS

**Iron Deficiency** Iron deficiency (ID) is the most prevalent nutrient deficiency in the world, and iron deficiency anemia (IDA) is probably the most prevalent disease on earth (WHO estimates more than 2.1 billion people). It is most prevalent in infants and young children in developing countries. It is estimated that more than 25% of infants worldwide exhibit IDA. Anemia is the last manifestation to appear with ID, since body iron stores are depleted prior to the occurrence of anemia. Symptoms of ID (even without IDA) are immune deficiencies, decreased muscle strength and working capacity, growth deficiency, and probable psychomotor delays. Long term studies of children with ID but lacking IDA to document improvement in mental and motor development with iron therapy have not been done. However, complete correction of both mental and motor development scores after iron therapy in IDA has been documented. However, the educational level of the mother clearly affects both the iron status and the mental development of the child in all of the studies in which it has been evaluated.

Of concern are the findings that in rats made IDA at different ages (newborn, young, adult) persistent deficiency of brain iron was found even after just a short-term deprivation in the youngest rats. Repeat studies found this to be age dependent. Young and adult rats could recover their brain iron after iron repletion, but newborn rats could not. The rats also showed an unrecoverable behavioral deficit related to the deficiency of striatal dopamine D<sub>2</sub> receptor, even after 6 months of treatment, despite normalization of the complete blood count. In 1998, it was shown in 6-month-old Chilean infants with IDA versus age-matched controls that they had delayed maturation of auditory brainstem responses. There are numerous reports of children with IDA in infancy and childhood with impaired learning and attentional problems for whom long-term iron therapy was ineffective. For example, the measurement of fetal iron status using umbilical cord serum ferritin and psychomotor testing at 5+ years of age in 278 children in Birmingham, AL, was studied. Skills tested included Full Scale Intelligence Quotients (FSIQ), language ability, fine and gross motor skills, attention, and tractability. Compared to children in the two median quartiles of cord ferritin results, those in the lowest quartile scored lower on every test and exhibited decreased language, fine-motor skills, and attention/ tractability. These results raise the concern that IDA during the course of early brain development, both prenatally and postnatally, is damaging.

Early studies in children documented changes in the regulation of emotions such as wariness, inattentiveness, hesitancy, and lack of involvement with tester or with testing stimuli among IDA infants. As is the case with PEM, IDA children demonstrate delayed motor skills with decreased scores on Bayley Scales of Motor Development. Long-lasting neuropsychological effects have also been attributed to IDA since 1974. After controlling for multiple variables, a decrement of 1 unit in hemoglobin has been associated with an increased risk of 1.28 (odds ratio) of mild-to-moderate mental retardation (MR). Recent studies are less definitive as the studies become more controlled, but information processing, behavior, and motor

## KEY POINTS

- Iron deficiency is the most prevalent nutrient deficiency in the world. It is most prevalent in infants and children in developing countries (estimates of more than 25%).
- When the educational level of the mother is included as a variable, it clearly affects both the iron status and the mental development of child.

## KEY POINTS

- In spite of limitations to most IDA studies, it is likely that an effect on brain function occurs acutely and probably chronically to IDA under 2 years of age. The extent of resultant delays is not well-known at this time.
- The greatest single worldwide preventable cause of brain damage and mental retardation is IOD. IOD or endemic goiter is the most common worldwide cause of congenital hypothyroidism.

development appear to be benefited by normal iron status.

Recurrent study design problems were present in almost all these studies on IDA. The primary problem is that there was no way to determine whether the internal family environment and caretaking processes among the IDA children were different from the normal children. In spite of these limitations of design and practicality, it is likely that an effect on brain function occurs acutely and probably chronically with early (<2 years old) IDA. IDA affects the availability of brain iron for biochemical reactions, neuronal processes, and neurotransmitter functions critically involved in the development of behavioral domains. IDA delays in timing of myelination and/or changes in brain D<sub>2</sub> dopamine receptor density may explain delays in motor development. Might IDA, therefore, cause alterations in attentional functions? Human studies remain difficult to interpret secondary to confounding variables and limitations on experimental design. Animal studies support important contributions to the understanding of mechanisms whereby specific nutrients affect neurochemistry and brain development. Despite the evidence to date, one should proceed with caution in making judgments with IDA, as we have learned from PEM. A causal link of IDA in infants and children to resultant psychomotor delays has not been well established at this time.

Iron and zinc are the most prevalent trace elements in the brain. Zinc is primarily found in the hippocampus, is important for morphogenesis of the CNS, and has a high turnover rate. Zinc appears to play a role in regulating the release of neurotransmitters (GABA and glutamate) and has been related to the storage of histamine in the hippocampus. Zinc deficiency has been shown to alter microtubule polymerization in the brain which might affect neuronal migration as well as produce hydrocephalus and neural tube defects in rats. Zinc-deficient animals also exhibit impaired learning, reduced activity, and poorer memory, possibly from the effect on the hippocampus. Behavior alterations in rats included reduced responses to stimuli, hypoactivity, and impaired cognition/visual discrimination learning. A

study in infants showed minor to no significant effect of zinc supplements on growth and development during 1 year in 109 term infants. There were nonsignificant improvement in motor scores and no significant differences in growth rates and size.

**Iodine Deficiency** WHO reports that among all countries, the greatest single preventable cause of brain damage and mental retardation is iodine deficiency (IOD). IOD or endemic goiter is the most common cause of congenital hypothyroidism worldwide. If this occurs in the first 2 to 3 years of life, the neurodevelopmental effects are severe and long lasting. Without treatment, affected infants become profoundly mentally deficient dwarfs. Thyroid hormone is critical for normal cerebral development, and effective treatment needs to be instituted promptly in infancy to prevent irreversible brain damage. When the onset of hypothyroidism occurs after 2 to 3 years of age, even when the child is symptomatic (deceleration in growth, fatigue, increased sleep, decreased attention span), the outlook for normal neurodevelopment after treatment is much better than in infants affected to the same degree.

In developing countries, IOD appears to contribute to delays in psychomotor development formerly attributed to PEM. Even more concerning are the probable countless numbers of persons with lesser degrees of neurodevelopmental delays due to IOD who go undiagnosed. The cretin syndrome which commonly includes mental deficiency, deaf-mutism, and spastic-rigid motor disorders can be correlated to anatomical locations; for example, cerebral cortex, cochlear, basal ganglion, and other cerebrospinal motor systems. A notable absence of ataxia, seizures, and hypothalamic dysfunction is documented. There is a lack of well-documented clinical-pathological studies on this topic. A summary of scattered findings reveals normal brain structure, normal gyral patterns in the cerebral cortex, decreased brain weights, reduced number of neurons, irregular arrangement of neurons, and dendrites which are reduced in branching and size. Recently reported T<sub>2</sub> signal abnormalities in the globus pallidus on brain magnetic resonance imaging (MRI) by DeLong are the first confirmation of basal ganglia abnormalities with IOD. All the cur-

rent data suggest that the critical time of IOD on the human fetal brain occurs between the second (>14th week) and third trimester. The duration of the exposure possibly plays a large role in the subsequent neurodevelopmental disabilities.

**Folic Acid Deficiency** Deficiencies of folic acid, vitamin B<sub>12</sub>, pyridoxine, vitamin E, and pantothenic acid have all contributed to the occurrence of neural tube defects (NTD) in rats. NTD are one of the most common

single primary defects in human development. Prevalence rates of NTD appear to be significantly reduced by the maternal ingestion of adequate amounts of folic acid prior to conception and during the initial stages of pregnancy. A clear mechanism for how folic acid protects against birth defects, including NTD, has not been determined (Case 2). Two theories have been proposed: (1) a methylation theory which results in decreased methylation of nucleic acids and

#### KEY POINTS

- Current data suggests that the critical time of IOD on human fetal brain development occurs between the 14th and 27th week of gestation.
- NTD are one of the most common single primary developmental defects in humans.
- Although the mechanism is unclear, prevalence rates of NTD are significantly reduced by maternal ingestion of adequate amounts of folic acid prior to conception and early in pregnancy.

#### CASE 2

A 21-year-old Hispanic woman was 19 years old at the time of her initial pregnancy. Her past medical history at that time revealed learning disabilities, but she graduated from high school. The family history was positive for learning problems in her mother and brother, but there was no family history of neural tube defects (NTD). She did not report taking vitamins or folic acid supplements during her pregnancy. Her obstetrical history included poor prenatal care, anemia, urinary tract infection, and elevated maternal serum alpha-fetoprotein (2.57 MoM). Her physical exam was within normal limits for an 18-week gestation with no evidence of obvious or subtle midline spinal defects. A fetal ultrasound at 18 weeks gestation revealed a myelomeningocele of the midthoracic spine, scoliosis, and bilateral talipes equinovarus deformities. The patient then presented at 22 weeks gestation in active labor with a breech presentation and delivered a 610-g stillborn male infant. Karyotype of fetal tissue was normal, 46,XY, and the open leaking myelomeningocele with lower limb deformities was confirmed. The patient now presents to the nurse midwife desiring to become pregnant again and is worried about the recurrence of a NTD in her next pregnancy.

Isolated NTD typically have a multifactorial inheritance pattern and result from the failure of closure of the neural tube in the third to fourth week of embryogenesis (gestation). The frequency of NTD in the world range from 0.5 to 3.2 per 1000 live births. There is a 3% to 5% risk of recurrence of NTD to the same couple in subsequent pregnancies. Although the genetic contribution to most NTD is poorly understood, the relationship between folate metabolism and NTD has been well established over the past 15 years. This is especially true against isolated NTD, but the exact protective mechanism of folic acid is not known. At the present time, it is recommended that all women of childbearing age should consume 0.4 mg of folic acid daily to prevent NTD. Concurrent malformations (facial clefting, limb defects, renal anomalies, cardiac defects) have also decreased in this same treatment population. Most studies show a reduction of isolated NTDs to almost zero in mothers who had a previously affected infant and who took folic acid in the preconceptional period during a subsequent pregnancy.

**Comment:** Neural tube defects comprise a variety of congenital malformations of the spine and central nervous system, including spina bifida, anencephaly, and encephalocele, which arise from incomplete closure of the neural tube during early embryonic development. Spina bifida refers to a spectrum of open and closed abnormalities of the vertebral column and spinal cord, including myelomeningocele, meningocele, and lipomeningocele. Occult spinal dysraphism is a milder variant of spina bifida characterized by failure of vertebral arch closure in association with tethering of the spinal cord. Abnormalities in the overlying skin or soft tissue, such as hair tufts, hemangiomas, or lipomas, can accompany the spinal abnormality, and neurologic symptoms may occur. In contrast, spina bifida occulta refers to incomplete ossification of the posterior vertebral laminae and occurs as a normal variant in otherwise healthy individuals. The average incidence of spina bifida in the United States is approximately 1 case per 1000 live births. However, significant regional variation has been observed.

**KEY POINTS**

- Many types of cells have vitamin D receptors, but it remains unclear at this time what this may mean to the developing central nervous system.
- The greatest single preventable cause of childhood blindness is vitamin A deficiency. Supplementation can prevent blindness.
- Brain development appears relatively resistant to nutritional deficiencies provided the psychomotor stimulation of the child is adequate.
- Usually PEM is not an isolated disorder but is associated with other nutritional deficiencies as well as inadequate psychomotor stimulation.

proteins, and (2) that folic acid maintains deoxyribonucleoside triphosphate pools (dNTPs) for de novo nucleic acid synthesis. New data support this second theory that birth defects are prevented by folic acid because of its role in providing precursors for DNA synthesis. No studies have investigated behavioral outcomes with regard to folic acid in early neonatal life.

**Vitamin D Deficiency** Precipitated by a resurgence of rickets in the United States due to vitamin D deficiency in breast-fed infants, the American Academy of Pediatrics now recommends a universal supplement of 200 IU of vitamin D for all infants not receiving vitamin D-fortified milk. Breast-feeding is the largest risk factor for a “low” or “low normal” serum 25-hydroxyvitamin D level (OHD). Since rickets is the end stage of vitamin D deficiency, other detrimental health effects of low 25-OHD levels would have been present for many months in these patients as well as in many who never clinically present with rickets. It is unclear what this may mean to a developing nervous system, but it has become clear that vitamin D and its effect on intestinal absorption of dietary calcium is essential to more than bone health. New research shows that many types of cells have vitamin D receptors. 25-OHD also moderates colonic and prostate cell proliferation, plays a role in susceptibility to tuberculosis and other invasive infections, and is implicated in contributing to autoimmune disorders such as diabetes. These are in addition to its well known effects on bone metabolism, dental caries, and growth.

**Vitamin A Deficiency** Vitamin A enhances neurogenesis and astrocyte differentiation by stimulating the proliferation of stem cells that are responsive to epidermal growth factor. It is possible, but not proven, that vitamin A deficiency might be associated with alteration in brain cell growth and differentiation.

The greatest single preventable cause of childhood blindness is vitamin A deficiency. Supplementation can prevent blindness.

**LONG-TERM FOLLOW-UP STUDIES FOR MALNUTRITION**

Brain development appears resistant to nutritional deficiencies provided the psy-

chomotor stimulation of the baby is adequate. In actuality, nutritional deprivation is usually associated with inadequate psychomotor stimulation. In addition, PEM is usually not an isolated disorder but is usually associated with other nutritional deficiencies which may include inadequate intake of essential fatty acids, iron, or even lead poisoning to confound the situation. Isolated maternal PEM appears to produce no permanent gross neurologic or intellectual deficit in the fetus, although recent reports continue to question this premise. The 1944 to 1945 Dutch famine long-term follow-up study, follow-up studies on children with cystic fibrosis and chronic gastrointestinal disease, as well as follow-up studies on small for gestational age infants, all indicate support for the lack of long-term psychomotor deficits in children malnourished early in life. The fetus has a remarkable resilience to PEM, especially exhibited by the developing brain to the presence of malnutrition. Even postnatal and post-weaning exposure to PEM in children who exhibit severe growth retardation and behavior/personality changes including apathy, inactivity, expressionlessness, and mutism appear to be reversed by refeeding. Although animal studies document associated changes in brain growth and function which even includes neurotransmitters (serotonin, histamine), there is little indication at this time that children suffer any severe permanent impairment of brain development if rescued from their malnutrition with refeeding.

Is there a “sensitive period” to malnutrition and its effect on physical and mental development? In particular, how does intrauterine or early postnatal exposure compare to exposure after 6 months of age? Developmental deficits appear to occur only in the subset of infants with intrauterine growth retardation (IUGR) who exhibit poor head growth in utero. In the National Collaborative Perinatal Project, which includes follow-up data at 7 years of heights and weights, infants with IUGR remained about 0.5 standard deviations (SD) less than infants born without IUGR; and for the whole project, IQ and Bender-Gestalt scores were lower in IUGR infants. However, there

were no significant differences in IQ or Bender-Gestalt scores between siblings born with and without IUGR. If head circumferences were significantly decreased, then IQ and Bender-Gestalt scores were significantly decreased. Other studies have shown that if weights at time of testing were taken into account, there was no additional effect attributable to timing of growth faltering. However, in these same children, a low weight at 2 years was associated with various developmental delays, whatever the timing of the weight faltering.

Exposure to nutritional deficiency during fetal life may be a risk factor for developing schizophrenia. This is suggested by a twofold increase in the incidence of schizophrenia in a birth cohort whose first 2 months gestation occurred during the Dutch famine 1944 to 1945. Although the numbers were small, in those with schizophrenia, MRI of the brain showed decreased brain volume. Nonschizophrenics exposed to the famine had increased brain abnormalities, in particular focal white matter hyperintensities. The white matter abnormalities in normal and schizophrenic patients could be the result of nutritional deficiency early in fetal life. Stunted early brain growth may also be a risk factor for schizophrenia.

A study of the long-term effects of severe undernutrition during the first year of life in Chilean high-school graduates showed that malnutrition at an early age may affect brain development, IQ, and scholastic achievement in school-age children. Particularly in developing countries, there are deficiencies of social sectors as well as health and nutritional factors which also need to be evaluated. Socioeconomic conditions were generally similar in this report. IQ was 25 points lower in the undernourished group. The amount of maternal schooling and undernutrition during the first year of life were independent variables with greatest explanation for IQ variance. However, environmental and genetic factors were not strictly quantitated in the study, although socioeconomic status was in the low or extreme poverty status for both groups. With birth weight low, there is a question of malnutrition effects in utero, but birth weight did not explain variance for either IQ or scholastic achievement.

Some investigators feel that intrauterine growth retardation has little effect on IQ, except when associated with deficits in head circumference, such as in this study (54.2 versus 56.2 cm,  $P < .01$ ). Undernutrition during the first year of postnatal life decreases the rate of growth of the head circumference, which is the most sensitive physical index of severe undernutrition during infancy. Some feel that the magnitude of this decrease is reliable in gauging the severity of the undernutrition. The lack of brain growth is probably secondary to reduced rates of neuronal cell division, reduced myelination, weight, nucleic acid, and protein content. None of the above findings can be definitive cause-and-effect-type relationships secondary to complex interactions of overall health issues, illnesses, energy level, rates of development, and the exacerbation of all the negative effects by poverty.

General chronic malnutrition as identified by stunting in the first 2 years of life was evaluated in Filipino children which included a 10-year follow-up evaluation. Children stunted between birth and 2 years of age had significantly lower cognitive test scores than nonstunted children, especially when stunting was severe. They also displayed reduced schooling secondary to delayed enrollments, higher absenteeism, and school failure. Both the stunted and nonstunted benefited from additional schooling. After multivariate adjustment, severe stunting at 2 years was associated with later cognitive delays. Children stunted at a younger age tended to be more severely stunted. Deficits at 11 years of age were smaller than at 8 years, suggesting that the negative effects may decline over time (Case 3).

Previous studies show interventions initiated as late as 3 to 4 years appear to be effective for improving cognitive outcomes (Table 2.4). Without intervention, children who are stunted early are probably at greater risk for adverse outcomes than those stunted later in life. Stunting is a measure of linear growth retardation. Early stunting was defined as a height-for-age Z-score (HAZ) at age 2 years of  $> -2$  SD below the mean based on the WHO reference data. Severe was a HAZ  $> -3$  SD; moderate was HAZ  $> -2$  and  $< -3$  SD. Stunting is a nonspecific indication of chron-

#### KEY POINTS

- In infants with IUGR, it appears that only those who exhibit poor head growth in utero manifest neurodevelopmental deficits.
- Exposure to prenatal nutritional deficiency may be a risk factor for developing psychopathology. How much other risk factors associated with malnutrition play a role is unclear.
- Undernutrition prenatally or during the first 2 years postnatally can decrease brain growth and make head circumference arguably the most sensitive physical index of severe undernutrition in children.
- In chronic malnutrition, identified by stunting in the first 2 years of life, severe stunting at 2 years is associated with later cognitive delays.
- Children severely stunted at an early age had smaller cognitive deficits at 11 years of age than they had had at 8 years of age, suggesting that adequate nutrition and additional schooling may reduce the negative effects over time.

**KEY POINT**

- Studies show interventions initiated as late as 3 to 4 years old appear to be effective for improving cognitive outcomes in children malnourished at an early age.

**CASE 3**

A 9-year-old Hispanic boy is struggling in a normal third-grade classroom. Psychological testing reveals his WISC-III Verbal IQ = 82, Performance IQ = 76, and Full Scale IQ = 79. Behavioral checklists suggest a diagnosis of attention deficit-hyperactivity disorder (ADHD) with decreased social adaptive interactive play/executive skills. There is no significant past medical history except he was adopted at 22 months of age from an orphanage in El Salvador. He had a history of resolved severe malnutrition and poor communication skills for greater than 1 year. He had been breast-fed as an infant. Laboratory values at adoption including a complete blood count, liver function, thyroid function, and urinalysis were normal except for a low hemoglobin = 10.1 g/dL. This is the only child of the adoptive parents, both of whom were schoolteachers. His adoptive mother stayed at home until he was enrolled in school.

On examination, his height, weight, and head circumference were at the 2nd percentile. His general physical exam was within the broad limits of normal with no dysmorphic features. His neurologic exam revealed inattentiveness with hyperkinesia, poor communicative/social skills, intact cranial nerves, mild incoordination of fine and gross motor functions, and normal reflexes.

This case is a realistic scenario and a significant world health problem. Severe malnutrition (protein, protein-energy, micronutrient types) during crucial times of early child growth and neurodevelopment appears not to produce large areas of irreversible brain damage, but long-term effects exist when compared to sibling-matched controls. If the malnutrition were severe enough to cause microcephaly, later IQ is about 15 points lower than predicted. Higher rates of long-term neurobehavioral issues [ADHD, pervasive developmental disorder (PDD)] are felt to be secondary to altered neurotransmitter responsiveness. However, adequate refeeding coupled with a nurturing environment with interactive play and reading time in the preschool years plays a more significant role in the ultimate neurodevelopment outcome than was thought in the past.

**Comment:** It appears that targeting women of childbearing age for nutritional assessment and/or supplements and the promotion of breast-feeding are the two most important cost-effective interventions for the prevention of childhood nutrition-related disorders. A normal diet along with the absence of food insecurity issues in a caring family environment ensures a child will reach his maximum potential unburdened by the effects of malnutrition.

ic malnutrition, although a broad range of insults may be represented such as prenatal malnutrition, micronutrient deficiencies postnatally, illness/infections, and/or inadequate parenting/attention from caregivers. About one-third of children stunted at or before 2

years of age experienced catch-up. The earlier and more severe the stunting, the less likely the catch-up. Adequate schooling for disadvantaged children who are stunted helps decrease their gap from normal the longer they attend school.

**TABLE 2.4** Dietary Management of Malnutrition

<p>Caloric intakes may need to exceed 120 to 150 kcal/kg/day</p> <p>Micronutrient deficiencies will also need to be corrected.</p> <p>Protein, energy, and other nutrient requirements vary with age, sex, and activity levels.</p> <p>Monitor growth and resolution of signs/symptoms of PEM, etc.</p> <p>Note: In postneonatal infants, appreciable weight gain can be documented in 1 week; 4 weeks are needed to document changes in length. Four to 8 weeks are needed to document a change in weight and height after 1 to 2 years of age.</p>
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## SUMMARY

Nutrients clearly play a direct role in the neurobiology of the CNS, but the actual relationships between specific nutrients and behavior/functional outcomes is unclear. There may be considerable redundancy in some brain systems to allow for normal function, but we are still learning if this is a valid concept. Environmental factors are constantly influencing neurodevelopmental and behavioral outcomes throughout any study on undernutrition that is done. There is considerable plasticity in the developing brain. Timing of any insult likely plays a role in the outcomes. If one nutrient alters another, it may be unclear which is generating the abnormal symptom; for example, zinc and copper alter fatty acid metabolism, so are the behavioral abnormalities secondary to low zinc or to the abnormal fatty acids? One of the most difficult challenges in behavioral neuroscience is that of translating changes in brain structure, neurotransmitter concentrations, or receptor activity into measurable outcomes. Nevertheless, the possibility that nutrient deficiencies early in life have adverse effects on neurodevelopmental and behavioral development, possibly by an effect on neurotransmitters or their receptors, needs a high priority for further studies, since some studies suggest that these adverse outcomes are irreversible despite nutritional recovery.

A wide range of micronutrients also affects neurodevelopment; the number of developmental stages susceptible to inappropriate supplies of those micronutrients is as diverse as the biochemical processes and tissue types which can be affected. It is challenging to propose a unifying hypothesis that could explain all the effects of micronutrient imbalance on CNS developmental programming throughout gestation. This concept is made even more complex by the effect of these micronutrient abnormalities on the expectant mother as well as directly on the developing fetus. Once again, and with few exceptions, the best approach at this time appears to be “what is good healthwise for the mother is good for the unborn child.” This simple concept is too frequently forgotten when focusing interventions on either the mother or child, rather than on both.

**TABLE 2.5** Common Nutritional Disorders and the Main Consequences of Malnutrition Throughout the Course of Life

### Pregnant and lactating women

#### Conditions:

Protein-energy malnutrition  
Iodine deficiency disorders  
Iron deficiency  
Folate deficiency  
Calcium deficiency

**Main consequences:** Insufficient weight gain in pregnancy; maternal anemia; maternal mortality; increased risk of infection; goiter; low birth weight/fetal death; neural tube defects

### Embryo/fetus

#### Conditions:

Protein-energy malnutrition  
Iodine deficiency disorders  
Folate deficiency

**Main consequences:** Low birth weight, microcephaly; stillbirth; neural tube defects

### Neonate

#### Conditions:

Protein-energy malnutrition  
Iodine deficiency disorders  
Iron deficiency  
Calcium deficiency

**Main consequences:** Growth retardation ± microcephaly; neurodevelopmental delays; anemia; rickets

### Infant and young child

#### Conditions:

Protein-energy malnutrition  
Iodine deficiency disorders  
Vitamin A deficiency  
Iron deficiency  
Calcium deficiency

**Main consequences:** Continuing malnutrition: wasted/stunted; neurodevelopmental delays; increased risk of infection; high risk of death; goiter, anemia; blindness; rickets

### Adolescent

#### Conditions:

Protein-energy malnutrition  
Iodine deficiency disorders  
Vitamin A deficiency  
Iron deficiency  
Folate deficiency  
Calcium deficiency

**Main consequences:** Stunted height, delayed growth spurt; delayed/retarded intellectual development; goiter; increased risk of infection; blindness; anemia; inadequate bone mineralization

The fear of food insufficiency is defined as a “food-insecure” household taken from United States data of the Third National Health and Nutrition Examination Survey in 1994. In these households, children are exposed to an environment in which there is a limited or uncertain availability of nutritionally adequate or safe foods. After adjusting for confounding variables, 6- to 11-year-old food-insufficient children demonstrated negative academic and psychosocial outcomes (arithmetic scores, repeating grades, psychologist visits, and difficult peer relationships). Although significant as an independent outcome, how much of a role does food insecurity also contribute to the outcomes of the truly malnourished in the world’s population?

Maturation of the CNS and consequent behavior depend on major factors which include (1) heredity (genes), (2) complexity and degree of environmental stimulation, and (3) adequate and balanced diet. Does (3) affect (2) and (1) as well as act inde-

pendently to affect outcomes? The severity and duration of the nutritional deficiency, developmental stage, biological condition of the child, socioeconomic context, amount of breast-feeding, small for gestational age birth weight, iron deficiency, iodine deficiency, and PEM are associated with long-term deficits in cognition, school achievement, and behavior (Table 2.5). However, all are also associated with poverty and poor health. It is difficult to establish that the long-term relationship is causal, and randomized treatment and long-term follow-up studies are needed. The only current study indicating definite long-term cause-and-effect consequences are on iodine deficiency in utero. Probably early childhood PEM has a similar relationship. A conclusion that appears valid based on multiple studies and this review is that interventions that improve the nutritional and social/personal environment and support and educate the children’s caregivers appear to be the most beneficial for the vast majority of children.

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Neurodevelopmental disabilities appear to occur only in the subset of infants who demonstrate poor head growth in utero when matched with normal sibling controls. There is little evidence to suggest that low birth weight limits IQ or motor development.



# NEUROLOGIC DISORDERS RELATED TO ALCOHOLISM AND MALNUTRITION

Ana Morales-Ortíz, Luis C. Rodríguez-Salinas, and Marco T. Medina

Alcohol is one of the major risk factors for burden of disease and social harm worldwide. The World Health Organization (WHO) estimates that there are about 2 billion people globally who consume alcoholic beverages and 76.3 million with diagnosable alcohol use disorders. From a public health perspective, the global burden related to alcohol consumption, in terms of morbidity and mortality, is considerable in most parts of the world. Alcohol consumption has health and social consequences through intoxication, dependence, and other biochemical effects. Overall, there is a causal relationship between alcohol consumption and more than 60 types of disease and injury. Alcohol causes 1.8 million deaths (3.2% of total) and a loss of 58.3 million (4% of total) of disability-adjusted life years (DALY) (WHO, 2002); neuropsychiatric conditions account for close to 40% of the 58.3 million DALYs.

Given alcohol's significance in world health, WHO has developed a database, the Global Alcohol Database (GAD), to provide a standardized reference source of information for global epidemiological surveillance of alcohol use and its related problems. According to this and the annual world health reports, alcohol has become a major risk factor for disease and disability in many countries across the world. The problems have to a large extent been stabilized in developed countries which have been exposed to substance use for decades, in contrast to many developing countries where alcohol use is rising rapidly and early onset and excessive drinking are reported consistently.

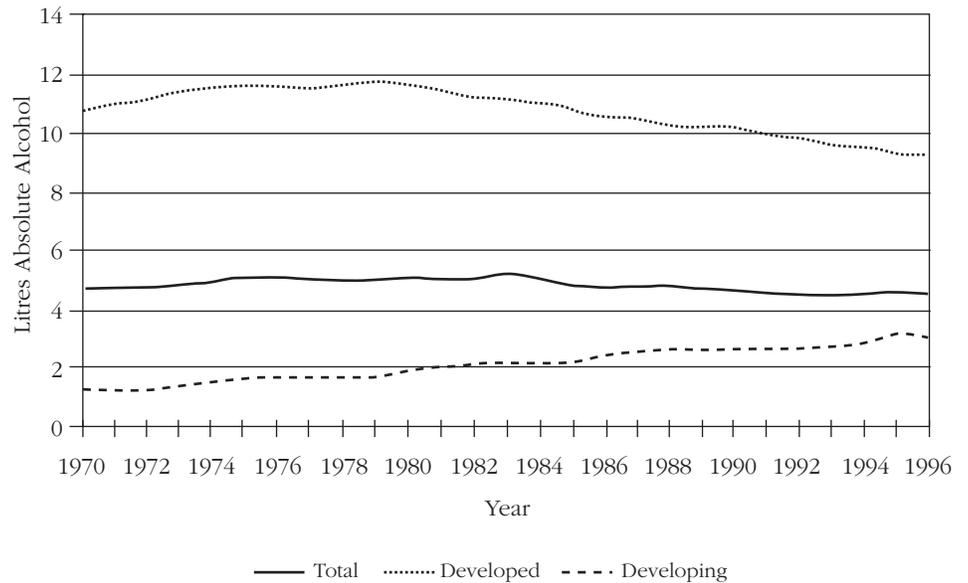
## ALCOHOLISM IN DEVELOPING COUNTRIES

Actually, alcohol consumption is the leading risk factor for disease burden in developing countries and the third largest risk factor in developed countries. The burden is not equally distributed among the countries. Data from the United Nations Food and Agriculture Organization (FAO) have indicated that recorded alcohol consumption in most developing countries is considerably lower than in most developed countries (Figure 3.1).

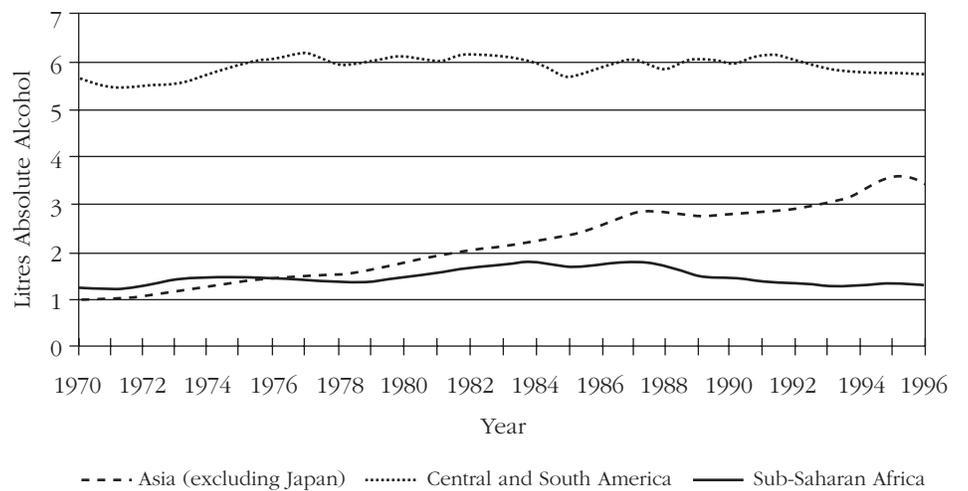
The main reason for this is the widespread poverty in many developing countries. Nevertheless, it must be borne in mind that recorded alcohol consumption figures underestimate consumption in most underdeveloped countries. It is clearly evident the trend toward decreasing consumption in most developed countries (with the exception of Japan and some parts of the former Soviet Union) since 1980 and the steady rise in recorded alcohol consumption in most developing countries. In the three macroregions of the developing world, recorded alcohol consumption has in general fluctuated with regional economic fortunes (Figure 3.2). In eastern and southeastern Asia, from the 1960s until very recently, alcohol consumption grew rapidly. Latin America and Africa saw increases from the 1960s through the early 1980s when global recession began to depress national economic development and alcohol consumption. The two regions showing recent and continuing increases in consumption are the Southeast Asian and the Western Pacific Regions. An analysis of trends in different macroregions suggests that economic development increases buying power, levels of alcohol use, and related harm.

## KEY POINTS

- Alcohol is one of the major risk factors for burden of disease and social harm worldwide through intoxication, dependence, and other biochemical effects.
- It causes 1.8 million deaths and a loss of 58.3 million of disability-adjusted life years (DALY).
- Alcohol is the leading risk factor for disease burden in developing countries and the third largest risk factor in developed nations.
- In the developing world, recorded alcohol consumption has in general fluctuated with regional economic fortunes. Financial development increases buying power, levels of alcohol use, and related harm.
- Risk factors that influence the pattern of drinking in developing countries are poverty, overcrowded environments, high levels of violence, unemployment, low education, changes in gender and age roles, and a high-intensity mass marketing and promotion of alcoholic beverages by multinational corporations.



**FIGURE 3.1** Recorded adult (age 15+) per capita consumption 1970–1996 by economic region (in liters of pure alcohol).  
Sources: FAO Statistical Databases; UNIDO 1998.



**FIGURE 3.2** Recorded adult (age 15+) per capita alcohol consumption in developing macroregions.  
Sources: FAO Statistical Databases, UNIDO 1998.

In Asia, Africa, and Latin America, urban populations increased from 16% to 50% of the total. Increased stressors and adverse events, such as overcrowded and polluted environments, poverty and dependence, high levels of violence, unemployment, low education, and deprivation, have deleterious consequences for mental health in general and substance use problems in particular, increasing the risk of heavy drinking. Half of the urban populations in low- and middle-income countries live in poverty, and 10s of millions are homeless; for instance, in Brazil, 77% of street children drink heavily. Other factors which have substantially affected patterns of drinking in developing countries include urbanization, changes in gender and age roles, and high-intensity mass marketing and promotion of alcoholic beverages by multinational corporations. Although alcohol is a major risk factor in several regions of the world, the Americas are unique in that alcohol surpasses smoking as the most important risk factor for burden of disease.

**NEUROLOGIC DISORDERS PRODUCED BY THE CONSUMPTION OF ALCOHOL**

Illnesses connected to consumption of ethanol are very common and reflect the extent of excessive consumption of alcohol in distinct countries throughout the world. Among the mechanisms by which alcohol produces neurologic disorders, it has been reported that there are a direct neurotoxic effect of alcohol or its metabolites, nutritional factors, and genetic predisposition.

The direct neurotoxic effects of alcohol and its acetaldehyde metabolites produce fatty acid stress which accumulates in diverse tissues producing susceptibility in distinct organs to the effects of alcohol. On the other hand, alcohol is a source of nonnutritious calories and produces malnutrition and vitamin deficiencies. Lastly, a genetic predisposition exists related to the development of alcohol dependency and neurologic complications, which is has been shown in children of alcoholic patients as susceptibility to develop those complications. In this sense, a genetic susceptibility that produces anomalies in distinct enzymatic systems could explain why one group of alcoholics develop a neurologic illness and others do not:

for example, a genetic alteration in the enzymatic system that metabolizes thiamine in a dependent individual would explain the predisposition among some alcoholics to develop Wernicke-Korsakoff encephalopathy.

In the majority of cases, we cannot say for certain which is the pathogenic mechanism responsible for the appearance of distinct neurologic illnesses related to alcoholism. In Table 3.1, a classification based on the possible pathogenic mechanisms of the distinct illnesses (which we used in the development of this article) is shown.

**RELATIONSHIP BETWEEN MALNUTRITION AND ALCOHOLISM**

Alcoholism is one of the major causes of nutritional deficiencies in the United States. Globally, the incidence of malnutrition in chronic alcoholics is estimated to be present in between 5% and 40% of patients. The interactions between nutrition and alco-

**KEY POINTS**

- In the Americas, alcohol surpasses smoking as the most important risk factor for burden of disease.
- Among the mechanisms by which alcohol produces neurologic disorders are a direct neurotoxic effect or of its metabolites, nutritional factors, and a genetic predisposition.
- Alcohol is a source of nonnutritious calories and produces malnutrition and vitamin deficiencies.
- A genetic predisposition exists related to the development of alcohol dependency and neurologic complications.
- Globally, the incidence of malnutrition in chronic alcoholics is estimated to be present in between 5% and 40% of patients.

**TABLE 3.1 Neurologic Complications Associated with Alcohol Abuse**

<p><b>Direct effects of alcohol</b></p> <p>Acute intoxication</p> <p>Fetal alcoholic syndrome</p> <p><b>Alcohol abstinence</b></p> <p>Symptomatic convulsive crisis</p> <p>Delirium tremens</p> <p><b>Disorders related to nutritional deficit</b></p> <p>Wernicke encephalopathy</p> <p>Korsakoff syndrome</p> <p>Pellagra</p> <p><b>Illnesses with unclear pathogenesis</b></p> <p>Alcoholic polyneuropathy</p> <p>Alcoholic myopathy</p> <p>Alcoholic amblyopia</p> <p>Cerebellar degeneration</p> <p>Marchiafava-Bignami disease</p> <p><b>Abnormalities due to hydroelectric alterations</b></p> <p>Central pontine myelinosis</p>
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**KEY POINTS**

- Alcohol can produce malnutrition through two mechanisms: a primary mechanism through which alcohol replaces other nutrients in the diet and a secondary mechanism in which it and its metabolites produce reduced absorption, digestion, and use of essential nutrients.
- Toxic metabolites generated through alcohol hepatic metabolism, interfere with the normal metabolism of substances, such as vitamins and other nutrients.

holism occur at many levels and are complex. Alcohol can produce malnutrition through two mechanisms:

1. A *primary mechanism*, through which the alcohol replaces other nutrients in the diet with reduction in the intake of carbohydrates, proteins, and vitamins
2. A *secondary mechanism*, where although the consumption of nutrients is adequate, the alcohol and its metabolites produce a reduced absorption, digestion, and use of the mentioned nutrients

Alcoholic beverages contain water, ethanol, variable amounts of carbohydrate, and little else of nutritive value. The protein and vitamin content of these beverages is extremely low except for beer. Heavy drinkers may derive more than half their daily calories from ethanol. Combustion of ethanol in a bomb calorimeter yields 7.1 kcal/g with a biological value less than that of carbohydrates on a calorie basis. Ethanol also increases oxygen consumption in normal subjects and does so to a greater degree in alcoholics, which produces an increase in metabolic rate, being a reason for their low weight. Suppression of appetite it also has been postulated as a cause of malnutrition, but it has not been studied adequately.

The metabolism of alcohol is produced by the enzyme alcohol dehydrogenase (ADH) and an enzymatic system called MEOS (microsomal ethanol-oxidizing system) through the liver, which generates toxic metabolites that are acetaldehyde, com-

posed to a great extent by oxygen. These products interfere with the normal metabolism of other substances: in the case of vitamins, this interference produces a deficiency particularly in the vitamin B group (B<sub>1</sub>, B<sub>6</sub>, and B<sub>12</sub>), niacin, and ascorbic and folic acids. This deficit is particularly noticeable in cirrhotic patients, although it can also appear in alcoholics without cirrhosis.

Alcohol consumption is associated with motility changes in the gastrointestinal tract and affects the digestion and absorption of nutrients. Diarrhea and steatorrhea frequently occur in alcoholics, mostly due to folic acid deficit but luminal bile salt deficiency may contribute.

As we will now see, in some cases, the relationship between a particular vitamin deficiency and the appearance of an illness is clear, as can be seen in Wernicke-Korsakoff encephalopathy or in pellagra. In other cases, the pathogenesis of the neurologic alteration is not clear, no specific nutritional deficit responsible for the same process has been found, and the probability that a direct alcohol toxic effect or other factors are involved is still unknown (Table 3.2). Finally, we have included other neurologic alterations related to alcoholism where the nutritional deficiencies can also have importance as it would be in hyperhomocystinemia, fetal alcohol syndrome, hepatic encephalopathy, or some hydroelectrolytical alterations which, in an indirect way, can be related to the nutritional state of the alcoholic patient.

**TABLE 3.2 Unspecified Neurologic Disorders Related to Alcohol**

Disease	Toxic alcohol effect	Pathogenic Mechanism	
		Malnutrition	Comments
Alcoholic Polyneuropathy	+++	+++ ( thiamine??)	Two different entities??
Alcoholic Myopathy	+++++	++	
Alcoholic Amblyopia	++	++++	
Cerebellar Degeneration	++	+++++(thiamine?)	Possible influence of a hydroelectric alteration.
Marchiafava-Bignami disease	++	++++	Unclear

## DISORDERS DEFINITELY ASSOCIATED TO NUTRITIONAL DEFICIENCIES

**Wernicke Encephalopathy** This disorder was first described in 1881 by Dr. Carl Wernicke in three alcoholic patients and was initially named *polioencephalitis hemorrhagica superioris* based on the neuropathological findings in those patients. It is produced by a thiamine (vitamin B<sub>1</sub>) deficiency, being most commonly seen in alcoholic patients. However, there are many other factors that can produce it and they should also be taken into account: hyperemesis during pregnancy, systemic cancer, gastrointestinal surgery, hemodialysis or peritoneal dialysis, prolonged parenteral nutrition with large quantities of glucose, severe malnutrition, nervous anorexia, and AIDS.

It is characterized primarily by the presence of a confusional state, ophthalmoplegia, and ataxia. The confusional syndrome is developed over a period of days or weeks and consists of lack of attention, apathy, disorientation, and loss of memory. The progression to stupor or coma is rare. The most common ocular anomalies are nystagmus (especially horizontal, and vertical is rarer and rotatory is extremely rare) and unilateral or bilateral palsy of lateral rectus muscles. Vertical palsy can also appear secondary to the affection of other extraocular muscles.

Ataxia is present due to compromise of vestibular nuclei and also the vermis. Clinically, progressive ataxia is common; however thumb-nose or heel-knee dysmetria is less common and dysarthria very rare. Of the neurologic symptoms, a peripheral neuropathy can also appear similar to other nutritional deficiency neuropathies. Other symptoms can be hypothermia, postural hypotension, and cardiac failure (Case 1).

Alcohol produces a thiamine deficiency through three mechanisms: food intake reduction, impaired intestinal absorption, or abnormal metabolism and hepatic storage of the vitamin. The deficit of thiamine produces a selective loss of activity of the ketoglutarate dehydrogenase thiamine-dependent enzyme, which is a precursor of the coenzyme thiamine phosphate that catalyses oxidation of pyruvate and ketoglutarate in coenzyme A. This is a limiting enzyme of the tricarboxylic acid cycle (Krebs cycle) and

### CASE 1

A 56-year-old Honduran man was found unconscious in his house. Among the disclosed precedents it was detected that he was a chronic drinker of at least 2 L of beer a day. He was taken to the hospital and after 4 to 5 hours he spontaneously woke up confused and agitated. The following day, he continued to be confused and showed horizontal diplopia and difficulty in walking. During the neurologic examination, a unilateral external rectus muscle and a serious gait ataxia were detected. His reflexes were reduced, and there was a reduction in the deep sensitivity of both legs. He was treated with thiamine given intravenously, and on the second day of treatment the ophthalmoplegia disappeared and the ataxia gait improved. After a few days, the patient completely recovered, being conscious and orientated.

produces an increase of lactic acid and excitotoxicity mediated by M-methyl-D-aspartate (NMDA) receptors. Recent evidence also shows the role of stress in the pathogenesis. Not all alcoholic patients develop Wernicke encephalopathy; thus it is thought that an individual susceptibility exists in relation to acquired or genetic alterations of the enzymes involved.

From the pathological point of view, symmetrical injuries are found in the paraventricular regions of the thalamus and hypothalamus, mammillary bodies, mesencephalic periaqueductal region, and the base of the IV ventricle, especially in the dorsal motor nuclear region of the vagus nerve, vestibular nucleus, and the superior vermis. The bilateral injuries in the mammillary bodies are usually a constant discovery during post-mortem studies.

A recent published study found that the classic syndrome mentioned earlier only appears in 10% of patients; thus it can be considered a frequently underdiagnosed syndrome. This possibility had already been established in previously postmortem analysis. In 1997, Caine et al., proposed some more workable diagnostic criteria than the classic preexisting triad for this syndrome (which only had 86% of accuracy) in order

### KEY POINTS

- Wernicke encephalopathy is most commonly seen in alcoholics, but there are many other factors that can produce it such as hyperemesis during pregnancy, systemic cancer, hemodialysis or peritoneal dialysis, prolonged parenteral nutrition with large quantities of glucose, severe malnutrition, AIDS, among others.
- It is characterized primarily by the presence of a confusional state, ophthalmoplegia, and ataxia.
- Alcohol produces a thiamine deficiency through three mechanisms: food intake reduction, impaired intestinal absorption, or abnormal metabolism and hepatic storage of the vitamin.
- Not all alcoholic patients develop Wernicke encephalopathy, thus it is thought that an individual susceptibility exists in relation to acquired or genetic alterations of the enzymes involved.
- Histopathologically, symmetrical injuries in the mammillary bodies, paraventricular region of the thalamus and hypothalamus, mesencephalic periaqueductal region, and the base of the fourth ventricle, vestibular nucleus, and the superior vermis are commonly found.

**KEY POINTS**

- Given the difficulty for a clinical diagnosis, in recent years, paraclinic diagnostic tests have been used to support the confirmation of this entity. Among the various laboratory tests, the notable indirect and direct biochemical tests are the measurement of erythrocyte transketolase enzyme (ETKA) or the effect of thiamine pyrophosphate (TTP).
- In MRI, signal alterations usually exist in T2 sequence in periaqueductal regions, mammillary bodies, thalamus, and periventricular zones; in some sequences, these alterations occur in 64% of the cases. The sensibility and the global specificity of the cerebral MRI in the diagnosis of Wernicke encephalopathy is 53% and 93%, respectively.

to try to improve the diagnosis of the illness and separate it from hepatic encephalopathy or from patients who have already shown Korsakoff syndrome.

According to these criteria, in order to diagnose Wernicke encephalopathy, the patient must complete at least two of following four criteria:

1. Nutritional deficit
2. Ocular motor alterations
3. Cerebellar dysfunction
4. Mental alteration or slight cognitive deterioration

Others have suggested a screening test (Table 3.3) to detect alcoholic patients with thiamine deficit. This test has been validated showing utility in detecting such patients; however, it must be evaluated more thoroughly.

Given the difficulty for a clinical diagnosis, in recent years a paraclinic diagnostic test has been used as a support in the confirmation of this entity. Among the various laboratory tests, the notable indirect and direct biochemical tests are the measurement of erythrocyte transketolase enzyme (ETKA) or the effect of thiamine pyrophosphate (TTP). All of these methods have the problem that they can be influenced by other factors.

Radiologically, in computed tomographies (CT) scan symmetrical hypodensities can be found in the diencephalon and in periventricular regions, although its normality does not discard the diagnosis. In magnetic resonance imaging (MRI), signal alterations usually exist in T<sub>2</sub> sequence in periaqueductal regions, mammillary bodies, thalamus, and periventricular zones. In some sequences,

**TABLE 3.3** Thiamine Deficiency Questionnaire

1. Frequency of consumption per year:
2. Carbohydrates
3. Fruit and vegetables
4. Meat, fish or poultry.
5. Frequency of making a complete balanced meal
6. Loss of weight in the past year (kg)
7. Weight gain in past year (kg)
8. Frequency of skipping meals due to lack of resources (weekly)
9. Frequency of loss of appetite and missed meals (per month)
10. Frequency of having breakfast (weekly)
11. Frequency of alcohol consumption
12. Units of alcohol consumed in a normal day.
13. Frequency of consuming 6 or more units of alcohol at once
14. Frequency of having "blackouts"(transitory deficits connected to memory that happen during periods of severe intoxication).
15. Frequency of drinking during the morning to eliminate abstinence symptoms (withdrawal symptoms)
16. Number of vomiting episodes during the last month.
17. Existence of other neurologic alterations related to malnutrition (polyneuropathy, amblyopia, pellagra, anemia, or subacute combined degeneration).
18. General state of health-related to nutrition.
19. Body mass index.

Source: Sgouros X et al., *Alcohol Alcohol.* 2004; 39(3):227-232.

these alterations occur in 64% of the cases. The sensibility and the global specificity of the cerebral MRI in the diagnosis of Wernicke encephalopathy is 53% and 93%, respectively. This low sensibility indicates that a normal MRI does not exclude the diagnosis either. Another technique of neuroimaging employed to evaluate these patients is single photon emission computed tomography (SPECT). In distinct series which have been undertaken, hypoperfusion at the frontal level and at a lesser grade in temporal and parietal lobes has been observed. The accuracy of this technique reaches 86%.

Treatment of Wernicke encephalopathy presents two important problems: first, as it was mentioned earlier in this chapter, the diagnoses of the disease is not easy, the complete clinical picture does not frequently appear, and the presence of an acute isolated encephalopathy in an alcoholic patient can have diverse etiologies, being difficult to differentiate between them. On the other hand, the treatment must be administered as early as possible due to the fact that, if not treated appropriately, up to 20% of patients with Wernicke encephalopathy could die and 86% could develop Korsakoff syndrome. Clinicians must be aware that in the acute phase, the injuries could be reversible. The most appropriate method of administration and correct dose of thiamine has been

discussed for many years. In alcoholics, thiamine intestinal absorption is reduced by up to 50% if it is taken orally, especially among those patients that have malnutrition. For this reason, the treatment must be administered intravenously with doses as high as 500 mg once or twice a day for a period of 3 to 5 days.

Given the diagnostic difficulties and the risk of this illness (low, but a real risk of anaphylaxia due to parental treatment), in 2002, the Royal College of Physicians in United Kingdom established a guideline about the urgent treatment of Wernicke syndrome. In this document, it is mentioned that patients at high risk of developing Wernicke encephalopathy must be treated with thiamine intravenously in the accident and emergency area of hospitals (Table 3.4). Those patients that have a low risk of developing Wernicke encephalopathy (well-nourished alcoholic patients who follow a correct diet and show no signs or symptoms of neurologic dysfunction), could be treated with 100 mg of thiamine, taken orally three times a day. The reason for thiamine treatment in these patients who are at low risk of the disease is that, among this mentioned group, between 30% and 80% of the alcoholics have low blood thiamine levels.

**Korsakoff Syndrome** S.S. Korsakoff, a Russian psychiatrist, described the disturbance of memory in the course of long-term

**KEY POINTS**

- Treatment of Wernicke encephalopathy must be administered as early as possible due to the fact that, if not treated appropriately, up to 20% of patients could die and 86% could develop Korsakoff syndrome. Clinicians must be aware that in the acute phase, the injuries could be reversible..
- In alcoholics, thiamine intestinal absorption is reduced by up to 50% if it is taken orally, especially among those patients who have malnutrition. For this reason, the treatment must be administered intravenously with doses as highest as 500 mg once or twice a day for a period of 3 to 5 days.

**TABLE 3.4** Prevention and Treatment of Wernicke Encephalopathy in Emergency Services

All patients with any evidence of chronic alcohol misuse and any of the following:

- Acute confusional syndrome
- Reduction in level of consciousness
- Ataxia
- Ophthalmoparesia
- Memory disturbance
- Hypothermia with hypotension.

Patient with delirium tremens syndrome

All patients with signs of chronic alcoholism who are hypoglycemic and who are going to be treated with glucose intravenously (these patients have a risk of acute development of Wernicke encephalopathy)

Source: UK Royal College of Physicians, 2002.

**KEY POINTS**

- Korsakoff syndrome consists of a severe affection of memory (anterograde and retrograde amnesia), sometimes accompanied by confabulation.
- Wernicke encephalopathy and Korsakoff syndrome are now considered to be different states of the same illness. The clinical difference between them is that in Korsakoff syndrome the conscious level is conserved but with an important memory defect and affected patients do not respond to treatment with thiamine.
- In a published study only 21% of patients who showed Korsakoff syndrome fully recovered, 26% did not improve at all, 28% showed slight improvement, and 25% improved quite well in a period of 2 months to 10 years of the treatment.
- Pellagra is a systemic disease secondary to niacin deficiency or its precursor tryptophan. It is not an illness exclusive to alcoholics and it can be seen among populations whose diet consists of mainly maize, as a consequence of malabsorption syndrome, or in those who consume certain drugs.

alcoholism in several articles at the end of the 19th century. He termed this syndrome *psychosis polynurritica*, believing that these typical memory deficits, in conjunction with polyneuropathy, represented different facets of the same disease.

This entity is a situation of cognitive deterioration that affects the memory of alcoholic patients in a selective manner through the appearance of one or more episodes of Wernicke encephalopathy. Now it is considered that Korsakoff syndrome and Wernicke encephalopathy are different states of the same illness (Wernicke-Korsakoff encephalopathy).

Clinically, the cognitive picture of Korsakoff syndrome is typical and consists of a severe affection of memory, primarily anterograde amnesia (a distinct difficulty in learning new facts and knowledge) and retrograde amnesia that can affect the patient for a variable period. Patients are usually disorientated, but the remaining cognitive functions are preserved. Some degree of confabulation may appear, although not necessarily constant (the patient fills the memory gaps with invented facts, without being conscious of his or her illness). If a careful neurologic exploration is carried out, a certain degree of nystagmus, ataxia, or polyneuropathy due to malnutrition usually can be found.

Pathologically, the injuries that appear in Korsakoff encephalopathy are similar to those of Wernicke encephalopathy with the only difference being that they are more chronic with more gliosis: there are necrotic injuries in the mammillary bodies, and periaqueductal, thalamic, and periventricular regions. It is believed that the injuries responsible for the memory impairment are located in the dorsal and medial nuclear level of the thalamus. In fact, injuries of another cause (hypoxia, tumor, or infectious) that produce lesions in those same zones can produce an indistinguishable Korsakoff encephalopathy syndrome. From the clinical practice perspective, the differential diagnosis of Wernicke encephalopathy isolated against a Wernicke encephalopathy, which has already developed Korsakoff encephalopathy fundamentally is based on the second clinical picture where the aware-

ness level is conserved, but there is an important memory defect with conservation of other cognitive areas and these patients do not respond to treatment with thiamine.

The treatment of Korsakoff syndrome is not really effective. It has been shown that treatment with thiamine is not fully effective once the amnesic deficit is established. In a published study, only 21% of patients who show Korsakoff syndrome fully recover, 26% do not improve at all, 28% show slight improvement, and 25% improve quite well in a period of 2 months to 10 years through treatment.

**Pellagra** Pellagra is a systemic disease secondary to niacin/nicotinic acid deficiency or of its precursor tryptophan. In underdeveloped countries, it continues to be a frequent nutritional deficit. It is frequently produced in alcoholics with associated nutritional deficit, although it is not an illness exclusive to this group, given that it also appears among populations that fundamentally consume maize (corn) as a source of carbohydrates: maize lacks nicotinic acid or tryptophan amino acid. It can also appear as a consequence of other alterations such as gastrointestinal malabsorption syndrome or can be associated with the consumption of some drugs: 5-fluoruracil, isoniazide, pirazinamide, chloramphenicol, 6-mercaptopurine, hydantoins, and phenobarbital.

Clinically, pellagra mainly affects three organs of the body: the gastrointestinal tract, the skin, and the nervous system. Classically, it produces the three D triad: diarrhea, dermatitis, and dementia. At the gastrointestinal level, it produces diarrhea, anorexia, nausea, vomiting, and abdominal discomfort. In advanced stages, the anorexia and diarrhea usually produce cachexia. The dermatological alterations are characterized by erythema and some reddish hyperkeratotic lesions that are distributed over a large part of the body, affecting the face, thorax, back, and the dorsal zone of the hands and feet. It is a bilateral and symmetrical pruriginous dermatitis that appears especially in zones exposed to the sun. In early stages, the lesions look similar to sunburn. Neurologic, in its initial stages, pellagra produces unspecific symptoms: photophobia, asthenia, depression, hallucinations, confusion, impaired memory,

and psychosis. At an advanced stage, the patient is affected with myoclonus, delirium, stupor, and coma, and this could lead to death. In neurologic exploration, spasticity and a Babinski sign can appear, which are clear signs of corticospinal tract involvement. Also, it can have the appearance of a polyneuropathy which is usually distal, bilateral, and symmetrical with sensory and motor symptoms and signs (Case 2).

From a pathological point of view, the neurologic injuries can be observed in the large motor cells (Betz cells), outer pyramidal cells, basal nucleus cells, motor nucleus cells of the indented cranial nerves, and in the posterior and lateral cords of the spinal marrow. The affected cells appear swollen and surrounded by eccentric nuclei and loss of Nissl particles (named "central neuritis").

The treatment is based on the administration of nicotinic acid. The necessary amount of nicotinic acid in the diet must be 6.6 mg/1000 kcal. Normally, nicotinic acid taken orally three times a day in doses of 50 mg is sufficient to treat patients with pellagra. It has been observed that the neurologic symptoms can be resistant to treatment even with prolonged management with niacin. For this reason, it is believed that possibly pellagra can be produced by a multiple deficit of vitamin B. In a classic experimental study carried out by Victor and Adams, who induced a pyridoxine deficit in monkeys produced pathological pellagra injuries, and also it is believed that a simultaneous thiamine deficit can be the origin of the polyneuropathy that appears sometimes in this illness.

Thus, the current treatment recommended is not only niacin but added vitamin B, zinc, magnesium, and a diet rich in calories. If pellagra is diagnosed and treated appropriately, the prognosis for recovery is excellent.

For the fact that the encephalopathy that appears in alcoholics is very often unspecific with symptoms of the illness sometimes not appearing, it is currently recommended that this alcoholic encephalopathy must be treated with multiple complex B vitamins, including pyridoxine, thiamine, and niacin. To prevent this illness, it is recommended a diet rich in niacin (eggs, dried fruit, red meat, fish, and pulses).

## CASE 2

A male Honduran patient, 40 years old, a farmer, illiterate, right handed, with a history of chronic alcoholism for 22 years is brought to the emergency room with a history of 1 week of being confused, drowsy with incoherent and irrelevant speech. He was not consuming alcohol for 2 weeks. His relatives mentioned that since approximately 3 months they have noticed that the patient presents a progressive deterioration of memory with lack of attention and insomnia. In addition, he has had watery diarrhea, three to four times a day in the absence of fever and vomiting and without responding to antibiotics. On examination, he was obtunded, dehydrated, and was hypotensive, tachycardic, afebrile, and pale, with severe malnutrition and some clinical stigmata of hepatic chronic disease without jaundice. A blackish dry skin on the dorsum of hands and feet was noticed. Neurologically, cranial nerves were normal. He was moving his extremities symmetrically without signs of corticospinal tract involvement. A slight asterixis was found. The rest of the neurologic examination was normal.

Total WBC count was increased with neutrophilic leukocytosis and with normal hemoglobin. Glycemia, blood urea, creatinine, and electrolytes were within normal limits. Liver function tests showed unconjugated bilirubinemia with normal liver enzymes. Serology for HIV was negative. X-ray chest and electrocardiogram were normal. CT scan and CSF analysis were also normal. On the basis of history and clinical features, an alcoholic liver disease, hepatic encephalopathy, grade II, and pellagra were diagnosed. Initially, the patient was managed with IV fluids, lactulose, B-complex vitamins, and also 150 mg of niacin daily. At the third day of being hospitalized, a nosocomial pneumonia with secondary septicemia was detected and aggressive antibiotic therapy was initiated, but the patient's general condition deteriorated rapidly and he expired 2 days later. Because of laboratory limitations, it was not possible to determine serum levels of alcohol, ammonia, thiamine, or niacin.

## KEY POINTS

- Classically, it is considered to produce a three D clinical triad: diarrhea, dermatitis, and dementia. At an advanced stage, patients can be affected with myoclonus, stupor, or coma..
- It has been observed that the neurologic symptoms can be resistant to treatment even with prolonged management with niacin. For this reason, it is believed that possibly pellagra can be produced by a multiple deficit of vitamin B.
- Currently, recommended treatment is not only niacin but added vitamin B, zinc, and magnesium and a diet rich in calories. If pellagra is diagnosed and treated appropriately, the prognosis for recovery is excellent.

**KEY POINTS**

- Neuropathy is the most frequent complication of alcoholism; depending on the diagnostic method employed, between 10% and 75% of alcoholics have polyneuropathy.
- The three pathogenic mechanisms that could influence the appearance of polyneuropathy in alcoholic patients are thiamine deficiency, the direct toxic effect of alcohol (toxicity caused by glutamate), and the general effect of malnutrition.
- Recent studies distinguish beriberi neuropathy from an alcoholic polyneuropathy because of the direct toxic effect caused by alcohol on axons.

**DISORDERS POSSIBLY ASSOCIATED WITH NUTRITIONAL DEFICIENCIES**

**Alcoholic Polyneuropathy** Neuropathy is the most frequent complication of alcoholism. Depending on the diagnostic method employed, between 10% and 75% of alcoholics have polyneuropathy. The origin of polyneuropathy in alcoholics has been widely debated. The three pathogenic mechanisms that could influence the appearance of polyneuropathy in alcoholic patients are: thiamine deficiency, the direct toxic effect of alcohol (toxicity caused by glutamate), and the general effect of malnutrition in such patients.

If the polyneuropathy is caused by thiamine deficit, it could be considered that the alcoholic neuropathy and beriberi (neuropathy caused by thiamine deficit) are the same entity. It has traditionally been considered in this way, with both neuropathies being considered the same. More recent studies distinguish beriberi neuropathy from alcoholic polyneuropathy because of the direct toxic effect caused by alcohol on axons (Table 3.5). Both entities are clinically very similar: they consist of a symmetrical motor-sensitive distal polyneuropathy that affects the legs more than the arms, especially at the distal level. Clinically, sensitive symptoms predominate, with paresthesias occurring which are normally painful and, in some cases, very severe and incapacitating. The cramps and a burning sensation are also very frequent. During exploration, a polyneuropathy

with diverse grades of strength loss, atrophy in the legs, loss of proprioceptive sensibility with superficial hypoesthesia at the sock level of the feet, and an absence or reduction of the reflexes is generally found. It is frequently associated with autonomic symptoms with paralysis of the vocal chords, dysphagia, pupil abnormalities, and hypertension. Hyperhidrosis in the hands and feet is very common too.

At a neurophysiologic level, conduction nerve studies show a reduction of response sensitivity with a slight reduction or normality in the velocity of conduction. The electromyogram (EMG) shows signs of denervation or reinnervation of the external inferior distal muscles. With respect to treatment, besides from avoiding alcoholic drinks, it seems prudent to add vitamin supplements for the possible influence of vitamin deficit in the pathogenesis (Case 3).

**Alcoholic Myopathy** Myopathy associated with alcohol can take two forms: acute or chronic myopathy. *Acute myopathy* appears very commonly in cases of large alcohol consumption, producing a sharp, painful debility that can appear in different areas. The creatine phosphokinase (CPK) usually occurs at very high levels. One must differentiate between acute alcoholic myopathy and that which appears in hypopotassemia and hypophosphatemia, which are also frequent in alcoholics but are usually less painful. Acute alcoholic myopathy can be confused with renal failure due to

**TABLE 3.5** Differences Between Beriberi Polyneuropathy and Alcoholic Polyneuropathy

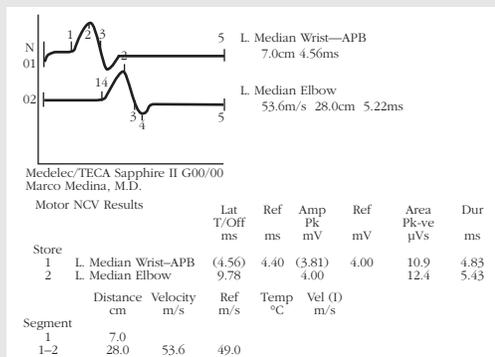
	<b>Beri-Beri Polyneuropathy Thiamine Deficit</b>	<b>Alcoholic Polyneuropathy Toxic alcohol effects</b>
<b>Etiology</b>		
Characteristics	Sensitive symptoms with little pain Pleasant autonomic symptoms Clear malnutrition	Sensitive painful symptoms Autonomic parasimpatic symptoms No signs of malnutrition
Neuropathology	Predominance of loss of myelinic fat fibers.	Loss of fine nonmyelinic fibers
Blood thiamine levels	Reduced	Normal

Source: Koike et al., *Neurology*, 2001; 56:1727-1732.

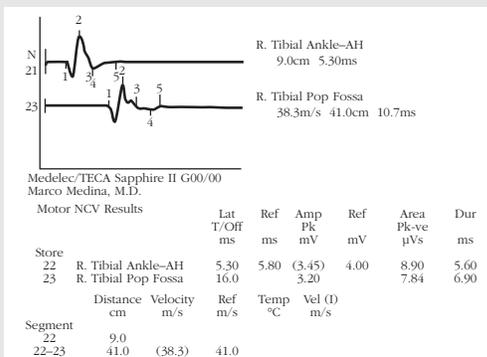
### CASE 3

A 44-year-old Honduran male patient, a heavy drinker, is hospitalized with a history of 10 days' suffering burning paresthesias in the hands and feet, and for 5 days, a rapidly progressive weakness predominantly in the lower extremities, without sphincter abnormalities, dyspnea, dysphagia, dysphonia, sialorrhea, diplopia, or facial asymmetry. During emergency evaluation, he was fully awake and orientated. Cranial nerves were normal (no ophthalmoparesis was detected), finding a superficial hyposensitivity in a "stock and glove" distribution along with apalesthesia on his feet. He had a flaccid and symmetrical paraparesis (+3/5) with generalized hyporeflexia and a bilateral flexor plantar response. Cerebellar maneuvers were normal in the upper extremities. Laboratory tests: CBC with mild anemia, glycemia: 99 mg/dL, blood urea, creatinine, and electrolytes were within normal ranges. GOT: 39 U/L, GPT: 32 U/L, AF: 74, PT and PTT were normal. CPK: 110 mg/dL; Albumin: 3.6. Thyroid function tests were also normal. B12 vitamin: >1200 and folic acid 3.2 (normal). Nutritional laboratory profile was not determined. Serology for HIV was negative.

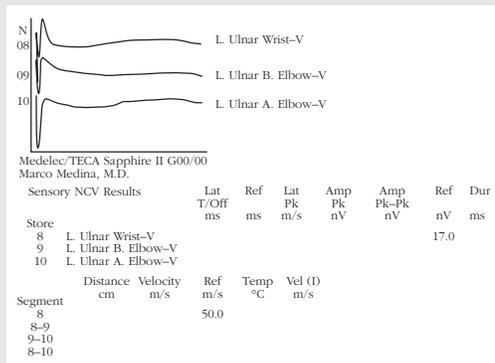
A peripheral nervous conduction study revealed both medium motor nerves with distal latency slightly prolonged. In the left medium nerve, the amplitude was also faintly diminished. The peroneal and tibial bilateral motor nerves had slow velocities of conduction, especially at the right leg. Besides, amplitudes were diminished, whereas in both nerves the distal latency was prolonged. Sensitive fibers of left median and ulnar nerves and sural bilateral were unexcitable. F wave study of bilateral tibial nerves showed minimal prolonged latency with the remaining parameters being in normal ranges. H reflex was unexcitable in both lower extremities. EMG showed mixed neuropathic signs (acute and chronic) in distal musculature of the upper extremities and in the whole musculature of lower extremities. This study was indicative of a sensorimotor polyneuropathy, of sensory predominance, with moderate axonemyelinic damage, probably of alcoholic-nutritional etiology.



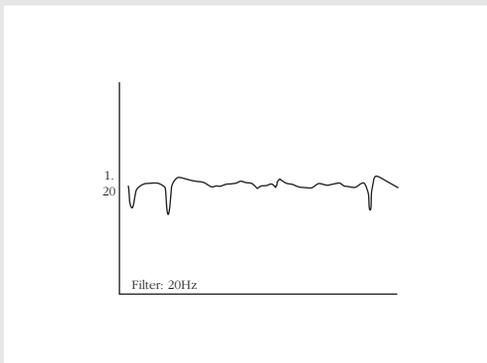
Left Median Motor Nerve



Right Tibial Motor Nerve



Left Ulnar Sensitive Nerve



Neuropathic Findings in Needle Electromyography (EMG)

**KEY POINTS**

- Acute myopathy appears very commonly in cases of large alcohol consumption, producing a sharp, painful debility that can appear in different areas. There are usually very high levels of CPK. The pathogenesis is a result of a direct toxic effect of alcohol, and treatment consists of withdrawal from alcohol intake, and then the patients note improvement.
- Chronic myopathy in alcoholics appears in 58% of patients. These alterations consist of a reduction of strength that primarily affects the proximal muscles and appears progressively through the years that patients chronically consume alcohol.
- Alcoholic amblyopia is a syndrome that occurs in malnourished chronic alcoholics and consists of an insidious loss of vision that increases over a variable period of time with affected visual acuity and a centrocecal scotoma. The condition is bilateral and symmetrical.
- The etiology of alcoholic amblyopia is unknown, although it is suspected that it is due to the nutritional deficit that is associated with chronic alcoholics.
- Cerebellar degeneration originating from alcoholism is considered the most common cause of acquired cerebellar degeneration.

myoglobinuria or cardiac alterations. The pathogenesis occurs as the direct toxic effect of alcohol which has been established as a nutritional cause, but still unexplained. The treatment consists of withdrawal from alcohol intake, after which the patients note improvements. It also seems that an increase in the caloric intake and diet influences the improvement of the condition.

*Chronic alcoholic myopathy* is very common. It occurs in 58% of alcoholic patients, and consists of a reduction of strength that primarily affects the proximal muscles and appears progressively through the years that patients chronically consume alcohol. The pathogenesis is unclear, but it does seem to be directly related to alcohol consumption. Experimental studies have shown that the alcohol has a direct effect on the skeletal muscle, producing an inhibition of muscle proliferation, slowing the muscle differentiation, and changes in the concentration of CPK.

Pathologically, it is a myopathy with a clear type II atrophy of fiber with reduction in the size of myocytes, oxidative alterations, and myocytolysis. Some practitioners have suggested a relation between the muscular effects and the quantity of alcohol consumed. The picture of malnutrition in this area continues to be debated. For some, the toxic effect of alcohol in the muscle is independent of the malnutrition, but its presence increases the toxicity to the muscle. In fact, a recent study showed that malnourished alcoholic patients have a greater loss of strength in deltoid muscles and a greater loss of muscular mass than well-nourished alcoholic patients. With respect to treatment, the benefits that are obtained in the myopathy resolution are evident when one stops drinking. It seems sure that increasing diet and caloric and vitamin intake improves the prognosis of this illness.

**Alcoholic Amblyopia** Alcoholic amblyopia is a syndrome that occurs in malnourished chronic alcoholics and consists of an alteration in vision produced by a specific injury of the optic nerve. It produces an insidious loss of vision that increases over a variable time period with affected visual acuity and a centrocecal scotoma. The condition is bilateral and symmetrical, and initially the

appearance of the optic nerve is usually normal, but peripapillary dilated vessels and hemorrhages have been described. If optic neuropathy progresses it can produce optic atrophy. Recent studies have discussed the precise localization of the primary lesion, which has not actually always been localized in the optic nerves and may possibly originate in other locations such as the macula, chiasm, or even the optic tracts.

The etiology of the syndrome is unknown, although it is suspected that it is due to the nutritional deficit that is associated with chronic alcoholics. The deficit cause has not been clearly determined but has been reported as being associated with vitamin B<sub>12</sub>, thiamine, folate, or riboflavin deficiencies. A similar optic neuropathy is produced in severely malnourished patients who are not alcoholics.

The treatment consists of complete vitamin supplementation, improvement in diet, and the avoidance of alcoholic drinks, which are measures that improve the condition in practically all cases. The level of recovery is related to the grade of visual loss and the chronicity of the injury: a prolonged deficiency can result in permanent loss of central vision.

**Alcoholic Cerebellar Degeneration**

Cerebellar degeneration originating from alcoholism is considered the most common cause of acquired cerebellar degeneration. It typically occurs after 10 years or more of alcohol abuse. The clinical picture is of a cerebellar syndrome that is developed in weeks or months with instability, truncal ataxia, and, in the case that a dysmetria is found, is more common in the legs than in the arms. The presence of dysarthria, hypotonia, or tremor is rare and nystagmus or ocular dysmetria are very unusual. Polyneuropathy can also be associated. Clinical differences between Wernicke's encephalopathy and cerebellar degeneration are shown in Table 3.6.

Actually, it is considered that chronic cerebellar degeneration is a persistent form of Wernicke encephalopathy, the same as Korsakoff dementia. Some patients who suffer Wernicke encephalopathy can develop chronic degeneration with cerebellar atrophy.

**TABLE 3.6** Clinical Difference Between Wernicke Encephalopathy and Cerebellar Degeneration

	Wernicke Encephalopathy	Cerebellar Degeneration
Instauration	Acute	Subacute
Symptoms		
Common	Ataxia, with ophthalmoparesis and nystagmus	Ataxia, dysmetria in lower extremities, and mild dysarthria
Less common	Dysmetria in lower extremities and dysarthria	No nystagmus or ophthalmoparesis
Evolution	Benign, responds to treatment	Severe, less response to treatment

Histopathological studies have revealed abnormalities similar to Wernicke encephalopathy with a distinctive atrophy of the superior and anterior parts of the vermis, compromising especially the Purkinje cells. The origin of the cerebellar degeneration is not known but the similarities with Wernicke encephalopathy suggest that thiamine deficiency can probably be an important factor in the pathogenesis. It has also been suggested that it can be secondary to hydroelectric alterations produced by alcohol. The possible influence of an indirect toxic alcohol effect is currently debated given that the cerebellar degeneration is not influenced by the daily quantity of alcohol consumed, and in experimental studies with animals, the cerebellar degeneration induced by alcohol produced other pathological injuries. Alcoholics with cerebellar degeneration may have an idiosyncratic sensitivity to the neuronal effects of ethanol. In CT scan and cerebral MRI, a cerebellar atrophy is always present. It must be emphasized that half of alcoholics showing atrophy do not seek medical help, and subclinical forms of the illness are currently being discussed. Given its possible relationship with Wernicke encephalopathy, these patients must be treated with thiamine administered by injection.

**Marchiafava-Bignami Syndrome** In 1903, Marchiafava and Bignami, two Italian pathologists, described three alcoholic men who died after having seizures and coma: in each patient, the middle two-thirds of the corpus callosum were severely necrotic. Through the years, about 250 cases have been reported in the medical literature. Most patients are alcoholic men.

The clinical presentation of this syndrome is variable. Some patients present with sudden onset of stupor or coma, and some present with seizures. Other patients have acute, subacute, or chronic onset of dementia and/or gait problems. Spasticity often complicates the gait disorder. Incontinence, hemiparesis, aphasia, and apraxia have been described. Neuropsychologically, patients can present apathy, indifference, irritability and mental slowness, similar to frontal dementia. Some cases occur in association with Wernicke encephalopathy.

The cause of the illness is still unknown. In the beginning, it was thought that it was a toxic effect of alcohol, but against this theory is the fact that it has been discovered in some nonalcoholic patients, suggesting that other factors must influence its pathophysiology. For this reason, currently it is considered that nutritional deficiencies are an important pathogenic mechanism in this condition, although the specific deficiency that could induce it has not been found.

Pathologically, there is a demyelination of the corpus callosum, particularly affecting the central region with respect to the anterior and posterior regions. The anterior and posterior commissures, the centrum semiovale, and the other white matter tracts (i.e., the long association fibers and the middle cerebral peduncles) may also be affected. Deep in the lesion, cavitation or cyst formation may be seen and corresponds to complete necrosis of all neural and glial elements. Patients with Marchiafava-Bignami syndrome usually do not have midline lesions, which are typical of Wernicke encephalopathy.

**KEY POINTS**

- Actually, it is considered that the chronic cerebellar degeneration is a persistent form of Wernicke encephalopathy with thiamine deficiency being an important factor in its pathogenesis.
- Histopathological studies have revealed abnormalities similar to Wernicke encephalopathy with a distinctive atrophy of the superior and anterior parts of the vermis, compromising especially the Purkinje cells.
- Marchiafava-Bignami syndrome implies a demyelination mainly of the corpus callosum and occasionally in other white matter tracts. Cavitation or cyst formation may be seen and correspond to complete necrosis of all neural and glial elements.
- Currently it is considered that nutritional deficiencies are an important pathogenic mechanism, although the specific deficiency that could induce it has not been found.

**KEY POINTS**

- More than 75 clinical and epidemiological studies have shown a relation between total homocysteine levels and coronary artery disease, stroke, peripheral artery disease, and venous thrombosis.
- Homocysteine is metabolized by two ways: remethylation, which is dependent on active forms of vitamin B12 and folic acid, and transsulfuration, which can be defective as a consequence of poor hepatic functioning. In alcoholic patients, the cause of hyperhomocysteinemia is the decreased metabolism of methionine secondary to vitamin deficiencies due to malnutrition and hepatic dysfunction.
- Fetal alcohol syndrome (FAS) is a birth defect syndrome caused by the mother's intake of alcohol during pregnancy. In order to receive a diagnosis of FAS, three criteria must be present: characteristic facial features, growth retardation, and central neurodevelopmental abnormalities.

In the acute phase, T<sub>2</sub>-weighted MRI commonly shows a hyperintense corpus callosum. As the lesions evolve, considerable necrosis may occur, and cystic areas of necrosis can be present in most or many regions of the corpus callosum (Figure 3.3). No specific treatment is available. Alcohol abstinence and a diet rich in vitamins and adequate caloric intake are recommended. The majority of the patients improve, although in some cases the dementia persists until the patient dies. Cases of spontaneous improvement have also been discovered.

**OTHER DISORDERS RELATED TO MALNUTRITION IN ALCOHOLISM**

**Hyperhomocystinemia** Hyperhomocystinemia is an independent risk factor for vascular diseases. More than 75 clinical and epidemiological studies have shown a relation between total homocysteine levels and coronary artery disease, stroke, peripheral artery disease, and venous thrombosis. High blood levels of homocysteine have also been linked with the risk of dementia and Alzheimer disease. Homocysteine (Hcy) is an intermediate product of the amino acid methionine and is metabolized by two path-

ways: remethylation, which recreates methionine, and transsulfuration, which converts homocysteine into taurine. Defects in the transsulfuration of the methionine can occur as a consequence of poor hepatic functioning, increasing homocysteine levels. Chronic alcoholics can show moderately high levels of homocysteinemia, which is more commonly seen when there is hepatic dysfunction.

The remethylation pathway transfers a methyl group to Hcy through methylcobalamin, an activated form of B<sub>12</sub> (which receives its methyl group from S-adenosylmethionine [SAME] or through 5-methyltetrahydrofolate [5MTHF], an active form of folic acid) or betaine (trimethylglycine). Nutritional imbalances, enzyme defects, alcoholism and disease states can lead to a decreased ability in converting cyanocobalamin to one of its active forms due to folate and/or vitamin B<sub>12</sub> deficit. In alcoholic patients, the cause of hyperhomocysteinemia is the decreased metabolism of methionine secondary to vitamin deficiencies due to malnutrition and hepatic dysfunction.

**Fetal Alcohol Syndrome** In 1968, Lemoine et al., first reported in France, a common pattern of physical and neurodevelopmental problems observed among the children of mothers with alcohol problems. Independent observation in the United States shortly thereafter led to the introduction of the term *fetal alcohol syndrome* (FAS) to describe the common features seen in these children.

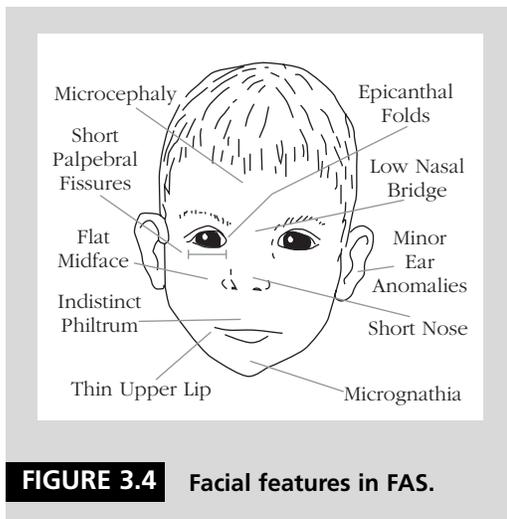
FAS is a birth defect syndrome caused by the mother's intake of alcohol during pregnancy. In order to receive a diagnosis of FAS, three criteria must be present:

1. Characteristic facial features (Figure 3.4).
2. Growth retardation such as lower birth weight, disproportional weight not due to nutrition, height or weight below the 5th percentile.
3. Neurodevelopmental abnormalities such as impaired fine motor skills, learning disabilities, behavior disorders, or a mental handicap (the latter of which is found in approximately 50% of those with FAS).

The mechanism of the fetal embryopathy resulting from ethanol ingestion



**FIGURE 3.3** Callosal damage in Marchiafava-Bignami syndrome: Sagittal nonenhanced T<sub>1</sub>-weighted image demonstrates a small, well-defined, and hypointense lesion in the genu of the corpus callosum.



**FIGURE 3.4** Facial features in FAS.

during pregnancy is not established. Some hypotheses have been postulated:

1. Alcohol is a teratogenic drug, which means it can cause birth defects when taken after conception. When a woman drinks alcohol, it reaches the placenta in a few moments and passes through the growing fetus producing a direct toxic effect.
2. The effects of ethanol ingestion during pregnancy on the concentrations of free amino acids in fetal and maternal plasma have been examined in murine models. It was found that the concentration of fetal plasma histidine was reduced by 50% as a result of maternal ethanol consumption. It has been suggested that fetal malnutrition in an essential amino acid, histidine, could impair fetal protein synthesis, producing FAS.
3. Some recent studies had explored as to whether an interaction between ethanol and vitamin A might potentially be the mechanism for FAS. The rationale for this hypothesis includes the known facts that (a) in adults, ethanol ingestion alters vitamin A metabolism and tissue distribution; (b) there are many phenotypic similarities between FAS and malformations of both vitamin A toxicity and deficiency; and (c) the vitamin A metabolite, retinoic acid (RA), is a potent mediator in embryogenesis and differentiation. One interaction that could possibly alter fetal development is that the synthesis of RA from

retinol, catalyzed by alcohol dehydrogenase, might be competitively inhibited by ethanol leading to RA deficiency. Controversy over this hypothesis continues, but it is clearly gaining experimental support.

FAS effects are permanent and cannot be outgrown. FAS babies and young children may have other specific distinguishable features: short stature, physical problems, including hearing defects, organ imperfections or bone problems, difficulty with eating, difficulty developing a regular sleeping schedule, difficulty learning how to walk, difficulty learning toilet training, impulsivity (i.e., running out into the street, going off with a stranger), and hyperactivity.

**Hydroelectric Disorders** Electrolyte alterations or their correction can produce neurologic disorders in alcoholic patients. Indirectly, the presence of these alterations can be due to malnutrition, thus they have been included in this chapter.

*Hyponatremia and Central Pontine Myelinolysis* Chronic hyponatremia produces changes in water levels in the brain, which reduces its osmolarity in order to adapt to hyponatremia. A rapid correction of hyponatremia produces a sudden rehydration that can lead to myelinolysis injuries. Central pontine myelinolysis is a neurologic complication that was first discovered with the generalized use of intravenous solutions for the correction of hydroelectric alterations. It consists of an injury in the central zone of the protuberance that appears in ill patients secondary to a rapid correction of hyponatremia. Extrapontine injuries can also appear localized at the thalamus, basal ganglia, anterior commissure, and corpus callosum levels. Sporadic cases of this syndrome without associated hyponatremia have also been discovered.

The effects of this syndrome are varied. A confused state, loss of consciousness, and coma can occur or paraplegia, quadriplegia, dysarthria, dysphagia, and compromise of other lower cranial nerves may occur. In some occasions, a locked-in syndrome can be produced. A cerebral MRI is useful as it characteristically shows the demyelination injuries in the protuberance and/or at an extrapontine level. Moreover, when continu-

#### KEY POINT

- The mechanism of the fetal embryopathology is not well established. Some hypotheses are teratogenic effect of alcohol, lacking of fetal histidine with impairment of fetal protein synthesis, and retinoic acid depletion secondary to a competitive inhibition of alcohol dehydrogenase by ethanol.
- A rapid correction of hyponatremia produces a sudden rehydration that can lead to a central pontine myelinolysis which is an injury in the central zone of the protuberance and that occasionally can be seen in other extrapontine zones.
- Clinically patients can develop a confusional state, loss of consciousness, and coma or paraplegia, quadriplegia, dysarthria, and dysphagia, and sometimes a locked-in syndrome can be produced.

## KEY POINTS

- The most prevalent factors in the appearance of myelinolysis in patients with treated hyponatremia are the correction of Na to normal or high levels in the first 48 hours of the treatment, a change in Na levels of more than 25 mEq/L during the first 48 hours, or the increase of Na levels to hypernatremia in those patients increasing the sodium concentration at not more than 2 mmol per liter per hour or 25 mmol per liter the first 48 hours.
- The presence of hypomagnesemia can occur in 30% of alcoholics. It is produced by a reduction of the tubular renal reabsorption of magnesium. It is accompanied by other electrolytic alterations that can lead to tremor, tetany, seizures, and coma.
- Hepatic encephalopathy is a neuropsychiatric syndrome which can occur in the clinical course of an acute hepatic insufficiency or in chronic hepatic failure. High-protein diets may precipitate hepatic encephalopathy; and protein restriction leads to malnutrition and enhances a negative nitrogen balance constituting a vicious cycle.

ing the evaluation with a series of resonances, the disappearance of the images confirms the recovery of the patient. The prognosis for these patients is poor given that it is associated with a high mortality. However, some patients can experience improvements after 1 to 4 weeks; as a result, the treatment for these patients must be aggressive as it could be a number of weeks before the patient begins to recover.

It has been shown that the most prevalent factors in the appearance of myelinolysis in patients with treated hyponatremia are the correction of Na to normal or high levels in the first 48 hours of the treatment, a change in Na levels of more than 25 mEq/L during the first 48 hours, or the increase of Na levels to hypernatremia in those patients, increasing the sodium concentration at not more than 2 mmol per liter per hour or 25 mmol per liter the first 48 hours.

*Hypomagnesemia* The presence of hypomagnesemia can occur in 30% of alcoholics. It is produced by a reduction of the tubular renal reabsorption of magnesium. Hypomagnesemia produces suppression of parathyroid secretion, and thus resistance to the action of this hormone as well as vitamin D suppression gives rise to hypocalcemia. It also induces loss of potassium through urine, giving rise to hypokalemia. All of

these hydroelectric alterations can lead to neurologic manifestations with the appearance of tremor, tetany, seizures, deterioration of consciousness, and coma. Magnesium supplements are crucial in the treatment of hydroelectric alterations in these patients (Case 4).

**Hepatic Encephalopathy** Hepatic encephalopathy is a neuropsychiatric syndrome which can occur in the clinical course of an acute hepatic insufficiency or in chronic hepatic failure. The recognition of this complication does not, at first glance, appear difficult, but differentiation from other neurologic syndromes related to alcoholism is important. Protein malnutrition is a frequent occurrence in liver cirrhosis, especially of alcoholic etiology. High protein diets may precipitate hepatic encephalopathy; protein restriction leads to malnutrition and enhances a negative nitrogen balance, constituting a vicious cycle.

Hrycewycz and colleagues, in France, investigated the possible contribution of protein malnutrition and zinc deficiency in the exacerbation of clinical hepatic encephalopathy. The investigators found that 88% of cirrhotic patients had low serum zinc. Low serum zinc was correlated with acute hepatic encephalopathy, hypoalbuminemia, and nutritional status.

## CASE 4

A 47-year-old man with a severe alcohol problem and diet lacking in proteins (without other important illness) has had a 3-month history of episodes of nausea and vomiting with general compromise and recurrent tremor. He was admitted on two occasions and gastrointestinal pathologies were monitored without showing major abnormalities. He looked for medical attention following an episode of nausea and vomiting similar to that described previously. In the emergency department, he had a generalized tonic-clonic seizure with a very intense posterior confusional syndrome, and he was admitted for study. During the analysis a 2.4 mg/dL level of hypopotassemia was found, similar to what had been discovered on previous times he had been admitted, as well as a 7.5 mg/dL level of calcium. An MRI revealed signs of vascular encephalopathy and an EEG showed diffuse slowing with signs of irritation at the bilateral temporal level.

On being admitted, the patient had nausea and vomiting with generalized tremor and an urgent analytic study showed calcium at 5.5 mg/dL and potassium at 2.3 mg/dL. These abnormalities were corrected and the patient improved. The following day, further magnesium studies were required which showed levels at 0.8 mg/dL. For this reason, 4 days of intravenous treatment was required, changing to oral supplements thereafter. Eventually the patient was discharged and improvements were observed over the following weeks after the treatment with magnesium, a varied protein rich diet, and alcohol abstinence.

Drinking leads to malnutrition and the lack of nutrients indirectly contributes to liver cell damage and also correlates with development of some of the serious compli-

cations of alcoholic liver disease (hepatic encephalopathy) and increased mortality (Case 5).

### CASE 5

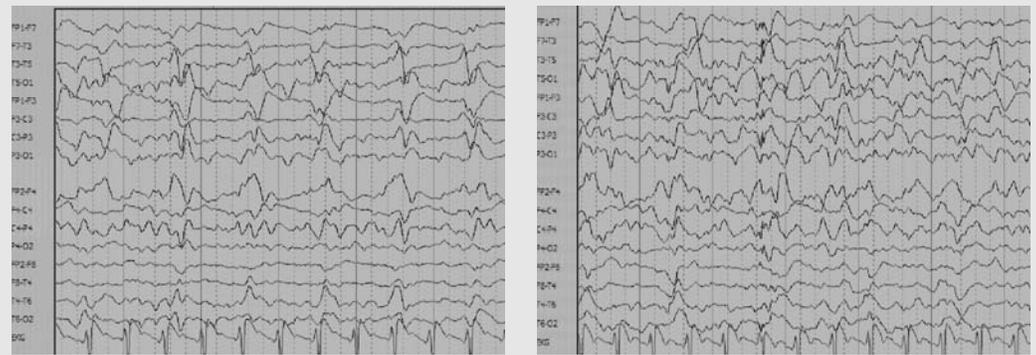
A 46-year-old woman, from a rural area of Honduras, illiterate, right-handed, with a background of chronic alcoholism for 10 years, is brought by ambulance, with a history that she was consuming alcohol severely in the previous 4 days. She was found unconscious in the street, not responding to verbal stimuli, with sialorrhea and evidence of sphincter incontinence. She was taken initially to a local hospital, but before the arrival there she began to seize constantly for approximately 30 minutes, which were generalized tonic-clonic seizures according to relatives' description and did not stop after administration 10 mg of diazepam. In the hospital, management for status epilepticus was initiated promptly with another dosage of diazepam and phenytoin 20 mg/kg, stopping convulsive activity. She was found to be euglycemic. She did not recover consciousness, and she developed a bronchoaspirative pneumonia and was sent to a specialized hospital. On admittance, she had a Glasgow Coma Scale of 6/15, pupils were symmetrical (3 mm), but hyporeactive and oculocephalic movements and corneal reflexes were weak, and an intermittent decerebrating posture in the left extremities was also observed with signs of bilateral corticospinal dysfunction and absence of meningeal irritation. She was hypoxemic (SatO<sub>2</sub> 80%) and she was immediately intubated and adapted to mechanical ventilation. The arterial pressure was normal, with a cardiac frequency of 120 per minute and respiratory frequency of 36 per minute. On physical examination, the patient was malnourished, pale, and without jaundice or signs of chronic hepatic disease.

Laboratorial studies: CBC: Hb:13.9 g/dL, Plt: 324,000, WBC: 15,100 (N: 84%, L: 10%, E: 3%). Coagulation tests were normal. Renal function was in normal limits. Glycemia: 142 mg/dL, GOT: 62 U/L, GPT: 14 U/L, AF: 100, total CPK: 405, total bilirubin: 0.41 mg/dL, electrolytes and urine analysis were normal. Because of laboratory limitations, it was not possible to determine serum levels of alcohol and ammonia. A later analysis of CSF also turned out to be normal.

CT scan showed moderate signs of diffuse cerebral edema, without focal lesions. A digital EEG was indicative of diffuse encephalopathy, showing a bilateral background theta activity (5 to 6 Hz), mixed with periodical delta activity (3 to 3.5 Hz), clearly asymmetrical, with polymorphic activity of major amplitude in the left hemisphere indicative of cortical/subcortical damage. A periodical pattern of bilateral triphasic waves of left predominance appear in several occasions during the tracing. Besides, a periodical burst-suppression pattern was evident in the left hemisphere, suggestive of hepatic and hypoxic-ischemic encephalopathy (in patient's context). Finally, the presence of interictal epileptiform activity was confirmed with recurrent spike-slow wave paroxysmal activity, beginning in the anterior temporary left regions (T3-F7) with secondary spread.

Based on the previous findings, the patient was diagnosed with a mixed encephalopathy (hepatic encephalopathy grade III-IV plus hypoxic-ischemic encephalopathy) and a convulsive status epilepticus secondary probably to alcoholic abstinence and bronchoaspirative pneumonia. An aggressive therapy with lactulose, manitol, alcoholic abstinence management, complex B/thiamine, phenytoin, and antibiotics for respiratory infection were initiated. In spite of these measures, the patient died 48 hours later.

*(continued on next page)*



A

B



C

A. EEG showing a bilateral background theta activity (5 to 6 Hz), mixed with periodical delta activity (3 to 3.5 Hz), asynchronous, clearly asymmetrical, with polymorphic activity of major amplitude in left hemisphere indicative of cortical/subcortical damage. Presence of interictal epileptiform activity was confirmed with recurrent spike–slow wave paroxysmal activity, beginning in the anterior temporary left regions (T3-F7) with secondary spread.

B. A periodical pattern of bilateral triphasic waves of left predominance and in the anterior regions of contralateral hemisphere.

C. A periodical burst-suppression pattern predominantly in the left hemisphere.

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# NEUROPHYSIOLOGIC FINDINGS IN MALNUTRITION

Rebeca Hernández-Toranzo, Heike Hesse, Luis C. Rodríguez-Salinas,  
and Marco T. Medina

Malnutrition results from alterations in the intake, digestion, absorption, metabolism, excretion, and/or metabolic requirements of dietary energy, protein, and other nutrients. As a result of these alterations, a deterioration of the different bodily systems takes place, with the nervous system being no exception. The central nervous system (CNS) as well as the peripheral nervous system (PNS) could be affected producing a variety of different neurologic syndromes.

The effects of malnutrition can be observed from the early stages of human development as well as in adults that have been exposed to faulty nutritional states. Although it is certain that the consequences of malnutrition are more severe in the fetus, newborn, suckling, and child, its effects do not lack clinical importance in the adult population.

Nutritional diseases of the nervous system have been carefully studied for more than 100 years, and many that were common in the last century now occur infrequently in developed countries, with the exception of specific nutritional deficiencies, most often related to alcohol abuse, inadequate dietary habits, and impaired absorption of dietary nutrients secondary to intestinal malabsorption syndromes. On the other hand, in underdeveloped or developing countries, the incidence of malnutrition is very high, including specific nutritional deficiencies, but more importantly as a global protein-calorie deficiency, related to poverty, parasitism, and low educational levels.

The neurologic abnormalities observed clinically in malnourished patients have been studied and documented by means of different neurophysiological tools, specifically nerve conduction studies, electromyography, brainstem auditory evoked potentials,

visual evoked potentials, somatosensory evoked potentials, motor evoked potentials, electroencephalography, and endogenous event-related potentials.

Many reports have been published of the effects of malnutrition in laboratory animals and humans due to protein-energy malnutrition (PEM), alcoholism, vitamin deficiencies (thiamine, pyridoxine, vitamin B<sub>12</sub>, folic acid, vitamin E), and specific mineral deficiencies, particularly iron. The focus of this chapter describes the central and peripheral neurophysiological abnormalities expressed during malnutrition.

## ELECTROENCEPHALOGRAPHY FINDINGS

Electroencephalography (EEG) activity has been found to be abnormal in several studies involving malnourished animals and humans. Alterations in cortical and hippocampal electrical activity, especially in theta activity, have been observed in the EEGs of malnourished rats. Altered ontogenesis of the EEG activity has also been observed, with initial delays in EEG amplitude, later development of abnormally high amplitudes in the power spectra, and altered sleep morphology. These findings could increase the susceptibility of seizures in animals.

In human patients, EEG abnormalities are significantly more frequent in poorly nourished children (Figure 4.1). Agarwall et al. pointed out EEG pattern abnormalities in 16 malnourished children in the form of slow and sharp waves, particularly in the frontal lobe, but also in the parietal and temporal lobes. The long-term effects of kwashiorkor was assessed in the EEG in children between 6 and 12 years old by Bartel et al., and this study showed significantly less alpha activity and more slow-wave activity

## KEY POINTS

- Malnutrition results from alterations in the intake, digestion, absorption, metabolism, excretion, and/or metabolic requirements of dietary energy, protein, and other nutrients.
- The central nervous system as well as the peripheral nervous system could be affected producing a variety of different neurological syndromes.
- In developed countries, nutritional disorders of the nervous system are most often related to alcohol abuse, inadequate dietary habits, and impaired absorption of dietary nutrients secondary to intestinal malabsorption syndromes.
- In underdeveloped countries, the incidence of malnutrition is very high, related to poverty, parasitism, and low educational levels.
- Agarwall et al. pointed out EEG pattern abnormalities in 16 malnourished children in the form of slow and sharp waves, particularly in the frontal lobe, but also in the parietal and temporal lobes.

**KEY POINTS**

- The long-term effects of kwashiorkor was assessed in the EEG in children between 6 and 12 years old by Bartel et al., and this study showed significantly less alpha activity and more slow-wave activity than in the EEG of the control group.
- Increased tonic theta power in the EEG may reflect a deficiency in the information-processing capacity of the CNS in alcoholics.
- In malnourished babies, modifications in the temporal pattern of delta and sigma band power during quiet sleep have been observed.
- Anorectic adolescents have shown an increased number of awakenings and wakefulness after sleep onset and a reduction of sleep efficiency and slow-wave sleep.



**FIGURE 4.1** An EEG recording of a 1- year-old alert female with severe PEM showing background activity of 4 to 4.5 Hz, amplitude between 30 and 60 µV, and frequent bursts of generalized high- amplitude delta activity between 3 and 3.5 Hz.

than in the EEG of the control group. Functional maturation of the EEG has been retarded in extremely low birth weight infants.

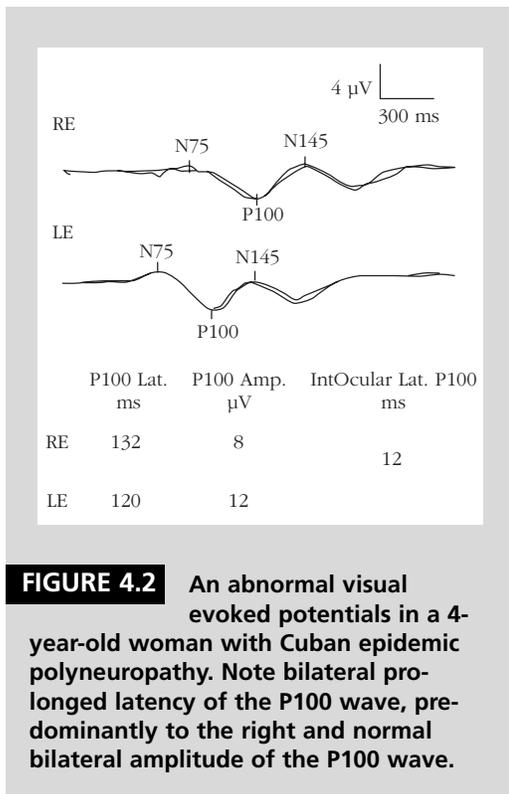
Increased absolute theta power was seen in alcohol-dependent subjects at all scalp locations by Rangaswamy et al. The theta log power increase in male alcoholics was prominent at the central and parietal regions and in female alcoholics at the parietal region when compared with the respective matched controls. Increased tonic theta power in the EEG may reflect a deficiency in the information-processing capacity of the CNS in alcoholics. The theta power increase may also be an electrophysiological index of the imbalance in the excitation-inhibition homeostasis in the cortex of these subjects.

The physiology of sleep has also been shown to be affected during malnutrition. Polygraphic recordings in rats have shown that prenatally malnourished animals spend more time in slow-wave sleep and substantially less time in rapid eye movement (REM) sleep compared to controls, a finding observed when the rats were adults and rehabilitated. In malnourished babies, modifications in the temporal pattern of delta and

sigma band power during quiet sleep have been observed. Anorectic adolescents have shown an increased number of awakenings and wakefulness after sleep onset and a reduction of sleep efficiency and slow-wave sleep, correlating to a weakness of slow-wave activity-producing mechanisms, according to spectral analysis results. The amount of slow-wave activity correlated positively with body mass index in these subjects. REM sleep physiology could also be altered during malnutrition. In malnourished rats, REM sleep deprivation is less tolerated than in control animals.

**SINGLE FIBER REGISTRATION**

A statistically significant decrease in the number of spontaneous firing of neurons in layers III, IV, and V of the cerebral cortex has been observed in malnourished rats, as well as decreased values in parietal and frontal cortices chronaxy. Other studies have shown altered ontogenesis of long-term potentiation in undernourished animals, with unknown implications to learning in malnourished subjects. To date, no study has been made to establish single fiber registration in humans with malnutrition.



**FIGURE 4.2** An abnormal visual evoked potentials in a 4-year-old woman with Cuban epidemic polyneuropathy. Note bilateral prolonged latency of the P100 wave, predominantly to the right and normal bilateral amplitude of the P100 wave.

## EVOKED POTENTIALS

Sensory evoked potentials are averaged responses to a repetitive sensory stimulus and can be used clinically or experimentally to evaluate the integrity and quality of conduction through central and peripheral pathways.

Motor evoked potentials are also now available to assess the motor pathways. A number of studies have been done with evoked potentials to understand the effects of malnutrition on animal and human subjects.

**Visual Evoked Potentials** Increased latency of the P100 visual evoked potentials (VEPs) is frequently observed in several degrees in vitamin B<sub>12</sub> deficiency and in alcoholic patients. Usually the abnormalities are bilateral and represent demyelination of the visual pathways (Figure 4.2).

**Brainstem Auditory Evoked Potentials** In rats, studies have established altered conduction in auditory systems secondary to protein-calorie malnutrition. The results showed that malnutrition caused a delay in the latency of all brainstem auditory evoked potentials (BAEPs) waves and the increases in the interpeak intervals of BAEP waves.

Abnormal BAEPs have been reported in children of different ages with moderate/severe PEM, iron deficiency anemia, and specific vitamin deficiencies. Altered BAEPs reflect functional brain immaturity and defects in myelination of auditory brainstem pathways. Described abnormalities included prolonged latencies of I, III, and V responses and prolongation of interpeak I to III, III to V, and I to V interpeak latencies.

**Somatosensory Evoked Potentials** Somatosensory evoked potential (SSEP) abnormalities have been reported in specific vitamin deficiencies, particularly in vitamin B<sub>12</sub> deficiency. Central sensory conduction time is the principal abnormality in upper and lower limb SSEP, suggesting dysfunction of the posterior columns. These findings imply that demyelination of the posterior part of the spinal cord and peripheral axonal degeneration might be the main pathological changes related to vitamin B<sub>12</sub> deficiency.

**Motor Evoked Potentials** Motor evoked potentials (MEPs) using electromagnetic transcranial stimulation of the motor cortex are now available to assess the motor pathways. In rats, using a postnatal malnutrition protocol with nutritional restoration, decreased motor conduction velocities have been reported. Prolonged motor conduction time has also been observed in malnourished children. Increased cortical thresholds, prolonged cortical latencies, and reduction in amplitudes of motor responses in malnourished children with PEM and in adult patients with vitamin B<sub>12</sub> deficiency have been reported.

**Endogenous Event-Related Potentials** The physiological bases of human perception and cognition can be studied by recording endogenous event-related potentials (ERPs) from the intact scalp. There are several endogenous components that are related with cognitive processing (P300), linguistic processing (N400), preattentive event-related potentials, movement-related potentials, contingent negative variation, and others.

It is well established that iron-deficient children have cognitive impairments, but electrophysiological testing supporting this data was until recently insufficient. An atten-

## KEY POINTS

- REM sleep physiology could also be altered during malnutrition. In malnourished rats, REM sleep deprivation is less tolerated than in control animals.
- Increased latencies of the P100 visual evoked potentials are frequently observed in several degrees in vitamin B<sub>12</sub> deficiency and in alcoholic patients. Usually the abnormalities are bilateral and represent demyelination of the visual pathways.
- Abnormal BAEPs have been reported in children of different ages with moderate/severe PEM, iron deficiency anemia, and specific vitamin deficiencies. Altered BAEPs reflect functional brain immaturity and defects in myelination of auditory brainstem pathways.
- Central sensory conduction time is the principal abnormality in upper and lower limb SSEP, suggesting dysfunction of the posterior columns in some vitamin deficiencies.
- Increased cortical thresholds, prolonged cortical latencies and reduction in amplitudes of motor responses in malnourished children with PEM and in adult patients with vitamin B<sub>12</sub> deficiency have been reported.
- Endogenous ERPs have demonstrated an attention deficit in iron deficiency children through a severely reduced P300, which recovers substantially after iron supplementation.

**KEY POINTS**

- P300 latency might be useful in judging the effectiveness of vitamin therapy in B12 deficiency and in differentiating dementia due to B12 deficiency from Alzheimer-type dementia.
- Cellular elements most commonly affected by nutritional deficiencies include the neuron itself and the myelin sheath. The result could be axonal degeneration as well as demyelination.

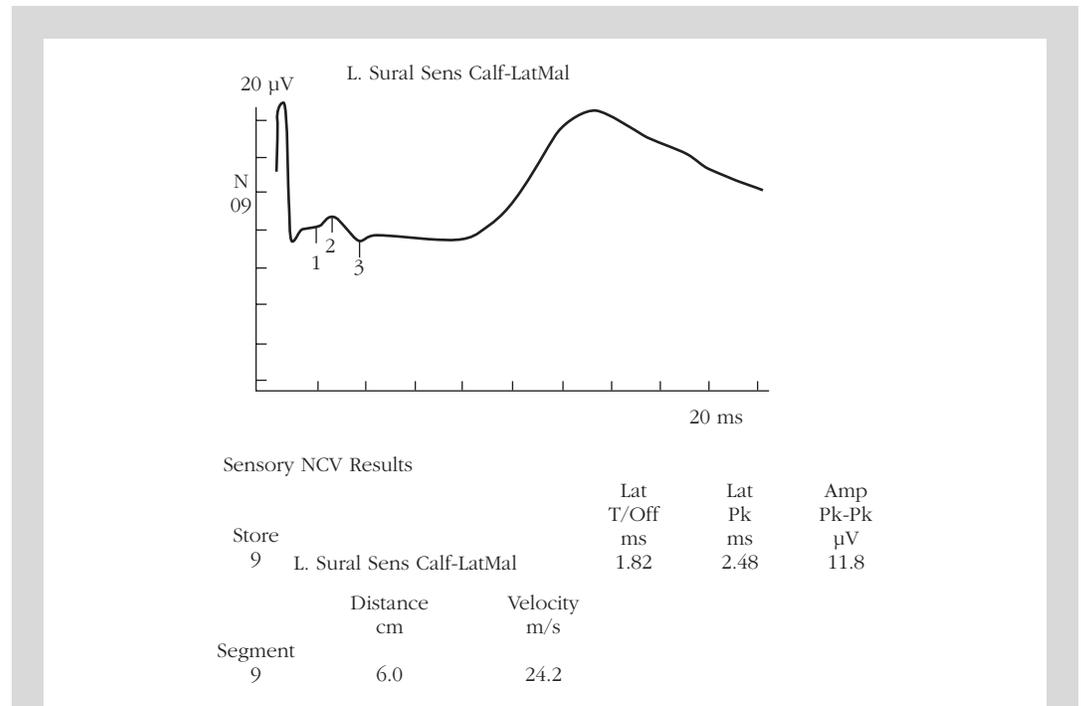
tion deficit is demonstrated in iron deficiency children through a severely reduced P300, which recovers substantially after iron supplementation. A patient with vitamin B<sub>12</sub> deficiency, dementia, and prolonged P300 latency was reported to recover after vitamin B<sub>12</sub> supplementation, with normalization of the P300 latency. Consequently, P300 latency might be useful in judging the effectiveness of vitamin therapy in B<sub>12</sub> deficiency. Similarly, improvement in P300 latency after vitamin supplementation may be useful in differentiating dementia due to B<sub>12</sub> deficiency from Alzheimer-type dementia in patients who happen to suffer from incidental vitamin B<sub>12</sub> deficiency.

Impairment in behavioral indicators of cognitive efficiency and in behavioral memory performance has been reported by recording the N400 component of the ERP

and a preattentive event-related potential component (mismatch negativity) in alcoholics respectively.

**NERVE CONDUCTION STUDIES AND ELECTROMYOGRAPHY**

Cellular elements most commonly affected by nutritional deficiencies include the neuron itself and the myelin sheath. In deficiency states that affect the neuron, the axon usually shows the first signs of damage and will be most severely affected. The distal ends of longer axons are affected first, since they are most susceptible to nutritional deprivation. The result is a dying-back neuropathy in which the distal ends of the peripheral nerves slowly degenerate, with the PNS being the most damaged, often resulting in clinical or subclinical neuropathy. With continued deprivation, the process moves toward the cell



**FIGURE 4.3** Sensory nerve conduction study of the sural nerve in a 3-year-old boy suffering from grade II chronic PEM, showing slowed nerve conduction velocity, mildly prolonged peak latency with normal amplitude. Additionally, the patient had reduced motor amplitudes and prolonged distal latencies on the right median and peroneal nerves; median motor nerve conduction velocity was also decreased. Median sensory distal latency was prolonged and the velocity was also mildly slowed. The diagnosis of a mixed sensory-motor polyneuropathy of nutritional etiology was made.

body. This type of neuropathic damage usually affects the largest and longest myelinated fibers and smaller unmyelinated fibers. The result could be axonal degeneration as well as demyelination.

The usual clinical manifestation is a painful distal neuropathy in which the patient experiences loss of proprioception, touch, temperature, and pain perception. There is often a burning sensation in the feet and hyperpathia and any contact with the affected limb may be perceived as unpleasant and painful.

Peripheral nerve conduction abnormalities have been observed in malnourished children and adults suffering from, marasmus or kwashiorkor, specific vitamin deficiencies, and/or alcoholism. Malnutrition results in alterations of the sensory fibers more frequently than the motor fibers and is predominantly axonal damage with secondary demyelination. The alterations of both

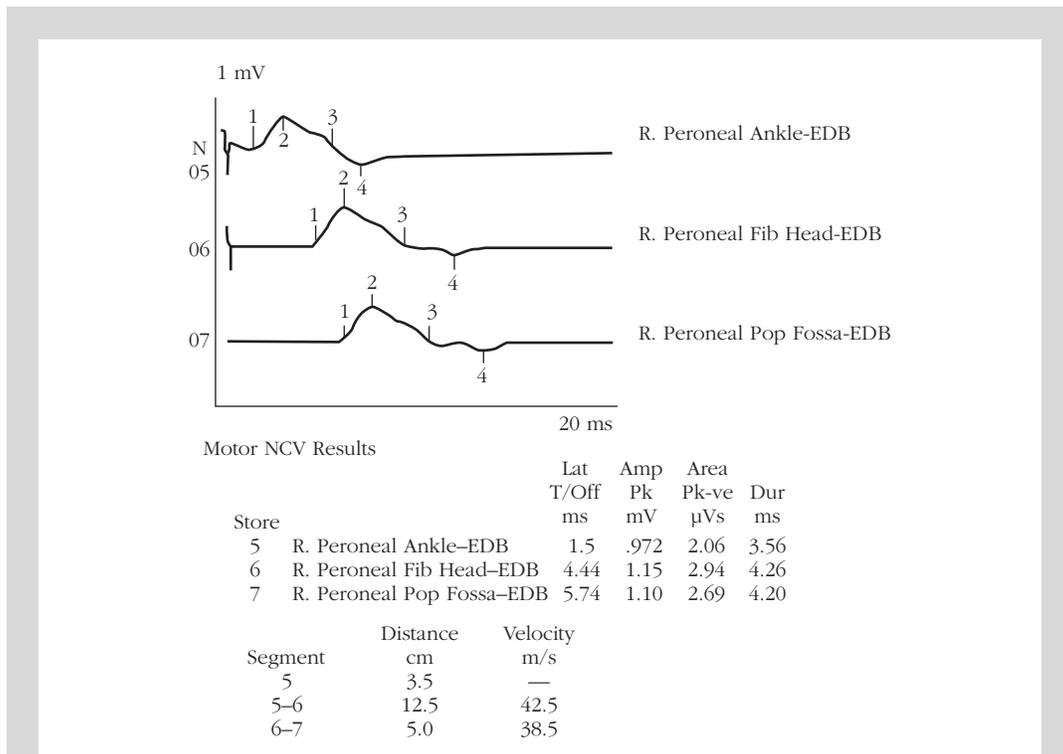
sensory and motor nerve conduction studies in some series have correlated clinically with abnormal reflexes, hypotonia, or delayed neuromuscular milestones (Figures 4.3 and 4.4).

Some malnourished children suffer additionally from muscle abnormalities. Primary protein-calorie malnutrition or secondary malnutrition from chronic disease can cause regression or stagnation of motor abilities, with hypotonia and amyotrophy.

As patients get older, clear amyotrophy and proximal muscle weakness may occur. These clinical observations were confirmed with abnormal electromyographic (EMG) and atrophy of type II fibers in muscle biopsies. Other myopathic EMG changes observed in malnutrition, and which have shown to be amenable to rehabilitation are reduction in amplitude and duration of motor unit potentials, and/or fibrillation. Muscle biopsies have also shown general

**KEY POINTS**

- Malnutrition results in alterations of the sensory fibers more frequently than the motor fibers and is predominantly axonal damage with secondary demyelination.
- Primary protein-calorie malnutrition or secondary malnutrition from chronic disease can cause regression or stagnation of motor abilities, with hypotonia and amyotrophy, which is confirmed with an abnormal EMG and atrophy of type II fibers in muscle biopsies.



**FIGURE 4.4** Motor nerve conduction study of the peroneal nerve in a 4-year-old boy suffering from grade III chronic PEM, showing mildly diminished amplitude of compound muscle action potential (CMAP), mildly slowed nerve conduction velocities, and normal latencies.

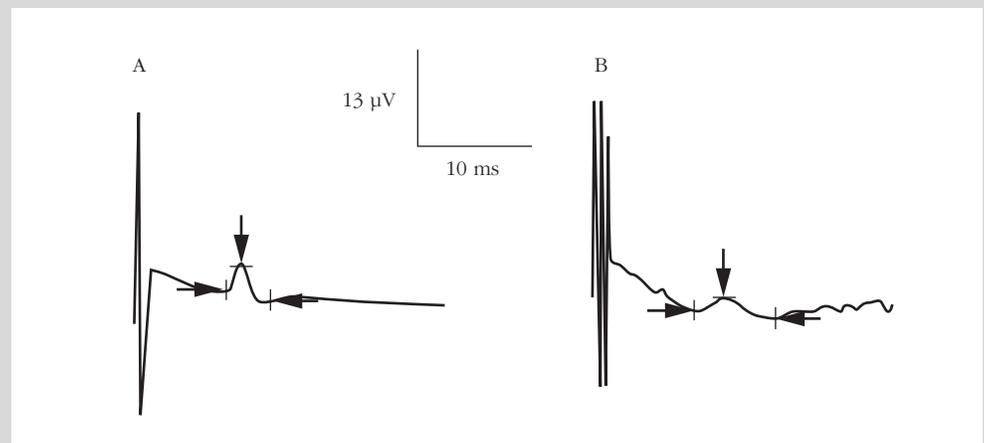
**KEY POINT**

- Neurophysiologic findings in the myopathy of the critically ill are difficult to differentiate from those observed in polyneuropathy, although normal sensitive action potentials and reduction of motor action potentials with direct muscle stimulation may help in this differentiation.

**CLINICAL CASE**

A 43-year-old woman from Havana City, Cuba, with a 3-month history of exhaustion, lost of approximately 9 kg of corporal weight, presenting blurry vision in both eyes, predominantly to the right, and a burning sensation on the hands and feet, was examined in Havana City during the second part of 1992. She had no personal or family history of interest, except for smoking one pack of cigarettes a day. Visual acuity was 0.6 in the right eye and 0.8 in the left. The fundoscopic examination revealed pale optic papillae, particularly on the temporal sides. Color vision examination using the Ishihara test was abnormal in both eyes, and campimetric examination showed a right central scotoma. Reflexes were abolished and sensitivity was diminished up to her calves. Tone and muscle strength were normal. BAEP and SSEP results were normal. Sensory nerve conduction latencies were prolonged and nerve conduction velocity was decreased on median and sural nerves bilaterally. Amplitudes of both sural nerves were decreased. The diagnosis of a mixed Cuban epidemic polyneuropathy, with moderate optic compromise, was made.

**Comment:** In the final months of 1991 and the beginning of 1992, a high incidence of diminished visual acuity was reported at the ophthalmology clinics in the western parts of Cuba. At the end of the first trimester of 1992, an epidemic neuropathy affecting primarily the optic nerves and less frequently the peripheral nervous system was diagnosed. By the end of 1992, the epidemic had spread to the whole island. The country was undergoing enormous economic difficulties, affecting the lives and nutrition of a big percentage of the population. Different possible etiologies were examined, including nutritional, toxic (alcohol and tobacco), metabolic, and infectious. Even though the low intake of nutrients and vitamins was responsible to a high degree, a multicausal hypothesis was proposed.



**FIGURE 4.5** A. An antidromic sural sensory nerve action potential (SNAP) in a control subject. B. SNAP in a 43-year-old woman suffering from Cuban epidemic polyneuropathy, showing diminished amplitude, prolonged latency, and slowed nerve conduction velocity.

fiber atrophy, obliteration of cross striations, streaming of Z bands, increased interfibrillary spaces, mitochondromegaly, and small-for-age fibers.

Neuromuscular impairments in critically ill patients has been well established, partic-

ularly polyneuropathy and myopathy. Many experts believe these abnormalities have a nutritional etiology. Electrophysiological studies show normal conduction velocities and reduced amplitudes of motor potentials. Neurophysiological findings in the myopa-

thy of the critically ill are difficult to differentiate from those observed in polyneuropathy, although normal sensitive action potentials and reduction of motor action potentials with direct muscle stimulation may help in this differentiation. The functional prognosis of primary muscle impairments tends to be good, but both polyneuropathy and myopathy resolve very slowly along weeks or months, with the possibility of an important residual deficit within two years in the most severe cases (Clinical Case).

## CONCLUSION

Global malnutrition and vitamin deficiencies in humans and animals do not always pro-

duce a definite neurophysiological syndrome, but the use of different electrophysiological tools allows the in-depth study of the functional changes in the nervous system secondary to malnutrition. The evidence shown before has led many researchers to think that malnutrition during the early stages of nervous system growth and maturation could cause a permanent suboptimal development, including important alterations to its plasticity and its implications in learning. The social impact of these sequelae on the least developed nations could be devastating.

## KEY POINT

- Global malnutrition and vitamin deficiencies in humans and animals do not always produce a definite neurophysiological syndrome, but the use of different electrophysiological tools allows the in-depth study of the functional changes in the nervous system secondary to malnutrition.

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