"Radiologically isolated syndrome"
Teaching Course 4
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"Radiologically Isolated Syndrome"

Outline
Diagnosing diseases in the preclinical stage!
Asymptomatic MS
Definition & Background & Overview
"Evolution from postmortem to premortem recognition"
"Radiologically isolated syndrome (RIS)"
Current concepts and clinical implications
Recent data and what to expect?

Diagnosing diseases in their preclinical stage!
Multiple Sclerosis

• The pathophysiological process of MS is known to begin many years before the diagnosis of the clinical disease...
• In most patients presenting with the first clinical episode of MS there are already several silent/asymptomatic old MRI lesions consistent with MS (and in some already atrophy and T1 black holes) indicating that the disease had already started some time ago...
• The presence of OCBs and elevated titers of IgG in the CSF, as well as detecting some specific biomarkers (before or at the time of Dx) are further evidence of ongoing early CNS neuro-inflammation and neuro-degeneration...

"Asymptomatic MS"

Definition
"Asymptomatic MS / Subclinical-MS"
When clinically silent disease is diagnosed by chance, either at autopsy or by MRI (then diagnosed as "RIS") or biologically - by CSF studies & other findings suggestive of an underlying probable demyelinating-inflammatory disorder! [in individuals with no MS related symptoms & signs]
Radiologically isolated syndrome (RIS)
is a form of "Asymptomatic MS"
But not all "Asymptomatic MS" cases are "RIS"

Asymptomatic MS
"Radiologically isolated syndrome"

Clinical problems!
The increasing use of MRI in various neurological problems or for other causes may reveal cases of "Asymptomatic Multiple Sclerosis - RIS" whose long term clinical behaviour is unknown but also some incidental nonspecific white matter abnormalities may be mistaken to be suggestive of MS and may cause some confusion for the unexperienced physician!

Disclosure
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Further questions...
Prior to the clinical diagnosis of MS...
• Does every MS patient have a pre-clinical "silent" phase?
• How early is the CNS involvement histologically?
• How widespread is it?
• How severe is it?
• Is there a time span for the active duration of the disease?
• How, when, why and in whom the subclinical disease stops?

Asymptomatic MS / RIS

Georgi W. Multiple sclerosis. Anatomopathological findings of multiple sclerosis in diseases not clinically diagnosed. Schweiz Med Wochenschr. 1961;91:605–15, 644 autopsies/12 cases (0.08 %) of unexpected MS findings

Asymptomatic MS – postmortem studies

Is it a very mild form of the disease?
Is it a self limited process?
Do number, severity & location matters?

• Is inflammation an early isolated event in asymptomatic MS? Is it mild?
• Does the MS lesion/s are limited in number and remain self limited in asymptomatic cases? No tissue destruction - no degeneration??

Asymptomatic MS – postmortem studies

Postmortem rate (prevalence) of "clinically silent" MS

Basel Institute of Pathological Anatomy*
• 66 / 15,644 autopsies cases of anatomically demonstrated MS
• (postmortem MS prevalence rate of 0.4 %)
• 54 had a confirmed clinical dx of MS or OND
• 12 had "incidental" autopsy findings - clinically silent MS
• rate of "clinically silent" disease 8.5% of a postmortem MS cohort

Danish MS Register of all autopsied cases of MS (1965-86)**
• clinically silent MS mean frequency: 0.08 %
• 40 persons / year die with clinically silent MS
• corresponding to 25% of deceased persons with an in vivo dx of MS

*Georgi, 1961; **Engell, 1989

Asymptomatic (Subclinical) MS

In asymptomatic family members of MS patients (and incidentally in anybody!)
• MRI: Lesions consistent with MS*
• CSF: OCB (+)**
• EP: abnormal***

In non-MS autopsies, sporadic cases of incidental lesions consistent with MS are found

For every diagnosed 4 – 5 "clinical MS patient" probably there is one other asymptomatic – undiagnosed individual with subclinical disease!

Asymptomatic MS and CSF findings

Asymptomatic first-degree relatives of MS patients may have oligoclonal bands in their CSF!

Asymptomatic MS / Subclinical-MS

Focal brain abnormalities indistinguishable from those of MS occur in asymptomatic first-degree relatives of MS patients.

No evidence of significant neuronal-tissue damage in asymptomatic individuals with radiologic findings suggestive of MS.

Asymptomatic MS and CSF findings

MS immunopathic trait

Asymptomatic first-degree relatives of MS patients may have oligoclonal bands (OCBs) in the CSF.

No evidence of significant neuronal-tissue damage in asymptomatic individuals with probable biologic findings suggestive of MS. (indicating immunopathic trait siblings)**

Asymptomatic Multiple Sclerosis

Asymptomatic lesions in patients with CIS/MS in most patients presenting with the first clinical episode of MS there will be several silent or asymptomatic old MS lesions that are consistent with MS.

Focal brain abnormalities indistinguishable from those of MS occur in asymptomatic first-degree relatives of MS patients.

No evidence of significant neuronal-tissue damage in asymptomatic individuals with radiologic findings suggestive of MS.

The Radiologically Isolated Syndrome Consortium (RISC) Core Group - 2009
**Radiologically Isolated Syndrome**

- No clinical symptoms or signs suggestive of MS
- MRI done for other reasons unrelated to MS
- An initial MRI fulfilling at least 3/4 Barkhof criteria for DIS

MRI – CNS abnormalities not attributable to another disease process or to any other medical condition

MRI anomalies not associated with any functional impairment

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**Radiologically Isolated Syndrome converting to clinical disease**

- **RIS - 5 and 10 years risk of developing an initial event consistent with MS**
  - Objective: To evaluate the 10-year risk for the development of the first symptomatic demyelinating event in a multinational cohort of RIS subjects


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**Radiologically Isolated Syndrome – dx criteria**

- No clinical symptoms or signs suggestive of MS
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**RIS - are there/will be MRI predictors for conversion to clinical MS?**

Macroscopic brain damage are similar in RIS and RRMS. However, the subtle tissue damage detected by MTI was milder in RIS than in RRMS. Cortical MTI lower in RRMS than in RIS and HC. Lower in RRMS*

Decreased brain NAA/Cr levels in a group of RIS subjects indicates that brain metabolic abnormalities suggestive of axonal damage can be significant even at this early stage. However, not all individuals with RIS have shown these abnormalities*


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**RIS - how early the disease process starts? ...and what that does mean?**

Cortical lesions (CLs) were found in 40% of asymptomatic subjects. CLs were not related to more pronounced cortical atrophy or worse cognitive performance.

Subjects with RIS with CLs had CSF (+) IgG OCBs & most had cervical spinal lesions on MRI - both risk factors for conversion. However, whether the occurrence of CLs in RIS can be interpreted as an indicator of possible clinical evolution to MS could not be established*

Giorgio et al. Neurology 2011

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**Results:** At 10 yrs >51% of pwRIS had converted to clinical MS

Age < 37 yr, positive CSF, spinal cord and PF lesions are risk factors for clinical evolution at 10yrs

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**Objective:** To evaluate the 10-year risk for the development of the first symptomatic demyelinating event in a multinational cohort of RIS subjects

Novel imaging techniques as biomarkers of neuroinflammation and neuroregeneration

The Radiologically Isolated Syndrome: in fact currently most of what we know is based on the good old conventional MRI!

But some work is emerging with more sophisticated MRI techniques...

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**Radiologically Isolated Syndrome**

"Radiologically Isolated Syndrome" Evidence for early neurodegeneration!

Azevedo et al Neurology 2015

Radiologically Isolated Syndrome Pathologically Defined as Demyelinating Disease*

- Three RIS patients where pathological examination confirmed CNS inflammatory demyelinating disease
- Presentations leading to imaging: intractable upper extremity pain, pituitary investigation for hormonal imbalance, and control volunteer for MRI study
- Mean age at initial MRI & biopsy: 36 years (range 29-43) [2F]
- Brain MRI showed a large (tumefactive) gad-lesion with additional non-enhancing white matter lesion/s in each
- Pathology confirmed inflammatory demyelinating disease indistinguishable from classic MS pathology in all three cases

*Keegan et al. AAN 2016 & Neurology. 2016 (Supplement)

Early changes in MS*

- Expression profiling of subcortical NAWM of MS brain tissue and control WM using microarray technology revealed the upregulation of a significant number of genes
- The MS brain is mounting a global defense against oxidative stress in order to preserve cellular function, even in areas remote from active inflammatory and demyelinating lesions
- This involves up regulation of genes that reflect a higher energy metabolism as well as genes involved in endogenous neuroprotection, which may affect all neural cell types

*Zeiss et al Brain Pathol 2009 & Schaeren-Wiemers, 2018

Radiologically isolated syndrome in children*

38 children with RIS (16 cites/countries) mean f/s age time: 4.8±5.3 yrs
A first clinical event consistent with CNS demyelination occurred in 16/38 children (42%) in a median of 2.0 yrs
Radiologic evolution developed in 23/38 children (61%)
The presence of OCB in CSF & spinal cord lesions on MRI were associated with an increased risk of a first clinical event

*Mahadev et al. Neuro Immunol Neuroinflamm 2017

Are all PPMS are primary progressive? Does RIS may present clinically as PPMS?*

Of the 453 subjects with RIS, 128 evolved to symptomatic MS during the follow-up (113 developed a first acute clinical event consistent with CIS/MS, 15 evolved to PPMS). PPMS prevalence (11.7%) and onset age (49.1±12.1) in the RIS group were comparable to other PPMS populations

Subjects with RIS evolve to PPMS at the same frequency as expected from general MS populations in an age-dependent manner. Besides age, unequivocal presence of spinal cord lesions and being male predicted evolution to PPMS. Our finding further suggest that RIS is biologically part of the MS spectrum

*Kantarci et al. ANN NEUROL 2016 79:288-294

Evidence for early neurodegeneration!

Alcaide-Leon et al Neuroimmunol Neuroinflamm 2018

This study found minimal micro structural differences in the SC of RIS, despite most participants having visible lesions and evidence of SC atrophy. MRI was lower in RIS, suggesting that inflammation and demyelination may be one of the only microstructural change detectable in the very earliest stage of MS, which is biexiting with known pathological mechanism in MS

Some structural changes but no atrophy!

Conclusion
The SC demonstrates minimal microstructural change suggestive of demyelination as well as inflammation in RIS. These findings are in contrast to established RIS and raise the possibility that the SC may play an important role in triggering clinical exacerbations in MS. Prospective follow-up of these cohort will provide additional insights on the role SC participates in the complex sequence of events related to MS disease initiation and progression.
“Radiologically Isolated Syndrome”
Is there early cognitive involvement?

However, it was also noteworthy that neither the individuals with RIS, nor their family members had noticed any signs of cognitive deficits or changes.

RIS patients have a similar cognitive profile to MS patients.

Q: Are these individuals, likely to be MS patients with an undiagnosed "clinically isolated syndrome" who present with cognitive dysfunction?


Cognitive involvement in MS!
Is it the early steps into the clinical disease?

Q: Is preclinical cognitive performance affected long before MS Dx?

- In a Norwegian study correlating the cognitive performance of all men born in 1950-59 that underwent conscription examination ages 18-19 to the Norwegian MS registry to identify those later developing MS, and randomly selected controls up to 20 years prior to first progressive symptoms.
- Are individuals with RIS, who are found to have a similar cognitive profile to MS patients likely to be undiagnosed CIS patients?
- But it’s also known that neither these individuals with RIS, nor their family members were aware of any sign of cognitive deficits or changes with any functional outcome.
- Is it possible that some clinical signs remain subclinical unless explored with special techniques and tools (similar to the demonstration of subclinical disease by imaging)?
- Therefore, such "sophisticated findings" may not always predict conversion to clinical disease and may correlate with a "subclinical disease state" that may remain as such for long periods or even a lifetime.

*Siiva A. Asymptomatic MS, Clinical Neurology, 2004

The MS prodrome - Does it exist?

More frequent use of healthcare (more hospital admissions / physician claims and prescriptions) in patients with MS than in controls in the 5 years before a first demyelinating event, according to health administrative data, suggests the existence of a measurable multiple sclerosis prodrome.

In two other studies MS patients reported higher rates of fatigue or depression in the years prior to the initial neurologic episode of their MS diagnosis compared with non-MS controls.


Prognostic biomarkers in radiologically isolated syndrome*

CSF CHI3L1 levels did not influence conversion to CIS and MS in people with RIS. But, CSF NFL levels and OCB were independent predictors of clinical conversion in patients with radiologically isolated syndrome.

Serum NFL levels were higher in pre-symptomatic PWMS compared to matched controls.

Both 6 years (med) & 1 year (med) before the first MS symptoms.

The clinical onset of MS was associated with a marked increase in NFL levels from a median level of 25 pg/ml to 45.1 pg/ml.


Radiologically Isolated Syndrome
Should it be treated with DMD or not?

- Current evidence doesn’t support early treatment in individuals with RIS*
- However, RIS patients may be followed by MRI every 6 mo in the first year, and then yearly for the next 2 years and at year 5 or until they develop clinical symptoms suggestive of MS!
- Individuals with "RIS", who have high risk factors (spinal cord lesions, younger age and male gender**) & continuous MRI activity may be considered for treatment trials at this stage!
- "Asymp MS/RIS" says something -probably important- and we should understand better & consider this concept/ phenotype, when evaluating and making treatment decisions for our MS pts!

Radiologically Isolated Syndromes

The "ARISE" study in which whether DMF delays the rate and onset of the first clinical event consistent with MS vs placebo in individuals with high risk RES had started in 2016 in the US*

*Okuda et al.

The "TERIS" study in which whether teriflunomide delays the rate and onset of the first clinical event consistent with MS vs placebo in individuals with high risk RES had started in 2018 in Europe**

**Lebrun et al.

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Marks Enes & Siva, M.S.T 2013 & Granberg et al, M.S.J 2013; **Okuda et al. Feb One, 2014