"Radiologically isolated syndrome"

Teaching Course 4
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- Received research grants from The Istanbul University Research Foundation & The Scientific and Technological Research Council Of Turkey

"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 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!

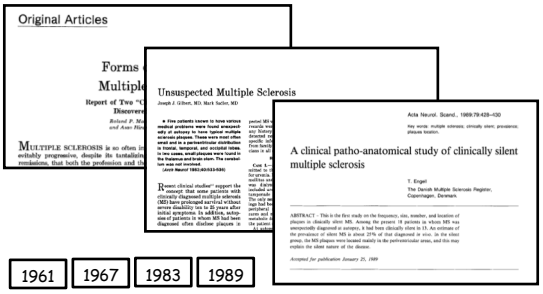
The increasing use of MRI in various
neurological problems or for other causes
may reveal cases of
"Asymptomatic Multiple Sclerosis - RIS"
whose long term clinical behaviour is unknown
but also some incidental nonspecific white matter abnormalities
may be mistaken to be suggestive of MS
and may cause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

Asymptomatic MS / RIS

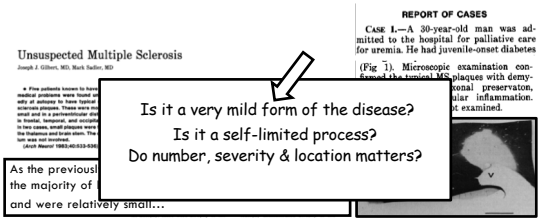
Further questions…
Prior to the clinical diagnosis of MS…

- Does every MS patient has 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 subcl/clinical disease stops?

Asymptomatic MS – postmortem studies

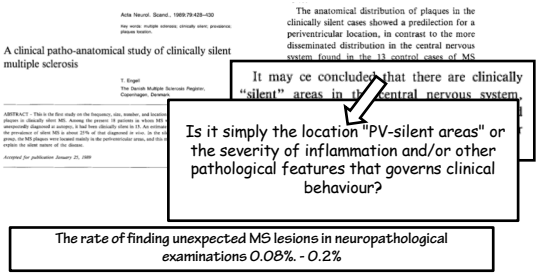


Asymptomatic MS – postmortem studies



- 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



The rate of finding unexpected MS lesions in neuropathological examinations 0.08% - 0.2%

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: 18% of a postmortem MS cohort

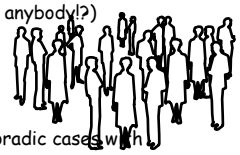
Danish MS Register of all autopsied cases of MS (1965-86)**
- clinically silent MS mean frequency: 0.08%
- 40 persons / year die with clinically silent MS
- corresponding to 25% of deceased persons with an in vivo dx of MS

*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 with 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!

*Uidehaag et al. JNNSP 1989; Lynch et al. Neurology 1990; Tienari et al. JNNSP 1992; Sadovnick, et al. Ann Neurol. 1993; Constantinescu et al. Mult Scler 1995; Fulton et al. Mult Scler 1999;
**Xian-hao & McFarlin DE. Neurology 1984; ***Nuwer et al. Ann Neurol 1985

Asymptomatic MS and CSF findings

Article abstract—Oligoclonal bands (OCBs) were examined in CSF from 23 normal controls, 8 cases of inflammatory neurologic diseases, 24 cases of noninflammatory neurologic diseases, 27 sporadic cases of MS, and the 29 MS twin pairs, by isoelectric focusing followed by silver staining or western transblotting and immunoperoxidase staining. These methods are sensitive enough to detect as little as 25 ng of IgG. OCBs were detected in the CSF of 34 of 35 twins with clinical evidence of MS and in the CSF of 12 of 17 clinically normal twins. In some of these normal twins, the presence of OCBs in CSF antedated clinical manifestations of the disease.

NEUROLOGY (Cleveland) 1984;34:769-74

Oligoclonal bands in CSF: Twins with MS

Xian-hao Xu, MD, and Dale E. McFarlin, MD

Cerebrospinal fluid findings in healthy siblings of multiple sclerosis patients

Article abstract—We studied six families in which two or more siblings were affected by MS. CSF analysis was available on 37 subjects: 9 with MS and 28 healthy siblings. Five of 28 healthy siblings (17.8%) had abnormal CSF immunoglobulins. These findings affect family studies of MS.

NEUROLOGY 1986;36:727-729

Pierre Duquette, MD, and Louise Charest, MSc

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

J Neurol (2000) 247 : 616–622
© Steinkopff Verlag 2000

ORIGINAL COMMUNICATION

Sara Haghighi
Oluf Andersen
Lars Rosengren
Tomas Bergström
Jan Wahlström
Staffan Nilsson

Incidence of CSF abnormalities in siblings of multiple sclerosis patients and unrelated controls

Acta Neurol Scand 2004: 109: 97–99 | ACTA NEUROLOGICA SCANDINAVICA

Cerebrospinal fluid markers in MS patients and their healthy siblings

Haghighi S, Andersen O, Odén A, Rosengren L. Cerebrospinal fluid markers in MS patients and their healthy siblings. Acta Neurol Scand 2004: 109: 97–99. © Blackwell Munksgaard 2003.

S. Haghighi, O. Andersen, A. Odén, L. Rosengren

*Xian-hao & McFarlin DE. Neurology 1984; *Duquette P & Charest L. Neurology, 1986
** Haghighi S, et al. J Neurol 2000; *** Haghighi S, et al. Acta Neurol Scand, 2004

Asymptomatic MS and CSF findings

MS immunopathic trait

Asymptomatic first-degree relatives of MS patients may have oligoclonal bands (OCB) in the CSF */**/***

19 % of ... CSF-OCBs (vs 4% ... tivity**

a moderatel... the MS group vs normal CS... c trait siblings (indicating ... damage)***

No evidence of significant neuronal-tissue damage in asymptomatic individuals with probable biologic findings suggestive of MS

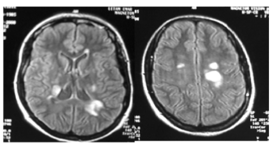
* Xian-hao & McFarlin DE. Neurology 1984; * Duquette P & Charest L. Neurology, 1986
** Haghighi S, et al. J Neurol 2000; *** Haghighi S, et al. Acta Neurol Scand, 2004

NFL: neurofilament light protein; GFAp: glial fibrillary acidic protein

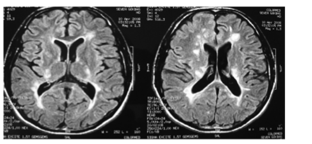
"Asymptomatic Multiple Sclerosis"

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» MRI lesions that are consistent with MS



23 yrs old F diagnostic MRI at onset with "ON"



27 yrs old M – diagnostic MRI at onset with "gait difficulty"

Asymptomatic MS / Subclinical-MS

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

A lesional MR ... ilar to that of

WM le... of NC

in NAW... all groups

indicating ... associated with widespread tissue damage commonly found in MS patients

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

DeStefano et al. Ann Neurol 2006

Asymptomatic MS
Radiologically Isolated Syndrome

Short report

Unexpected multiple sclerosis: follow-up of 30 patients with magnetic resonance imaging and clinical conversion profile

See editorial commentary, p 112

Incidental MRI anomalies suggestive of multiple sclerosis

The radiologically isolated syndrome

D.T. Okuda, MD
E.M. Mowry, MD
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E. Waubant, MD, PhD
S.E. Baranzini, PhD
D.S. Goodin, MD
S.L. Hauser, MD
D. Pelletier, MD

ARTICLE | Multiple Sclerosis 2009; **00:** 1–10

Multiple sclerosis risk in radiologically uncovered asymptomatic possible inflammatory-demyelinating disease

*A Siva[1], S Saip[1], A Altintas[1], A Jacob[2,**], BM Keegan[3] and OH Kantarci[3]*

Background Natural history of patients with incidentally discovered lesions that fulfill magnetic resonance imaging (MRI) criteria for multiple sclerosis (MS) in the absence of objective clinical symptoms suggestive of central nervous system (CNS) inflammatory-demyelinating disease is not well defined.

Lebrun et al JNNP, 2008
Okada et al Neurology, 2009
Siva et al Multiple Sclerosis, 2009

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

Radiologically Isolated Syndrome – dx criteria*

No clinical symptoms or signs suggestive MS

MRI done fo… …lated to MS

An initial MRI fu… …criteria for DIS

MRI – CNS abnor… …another disease process o… …condition

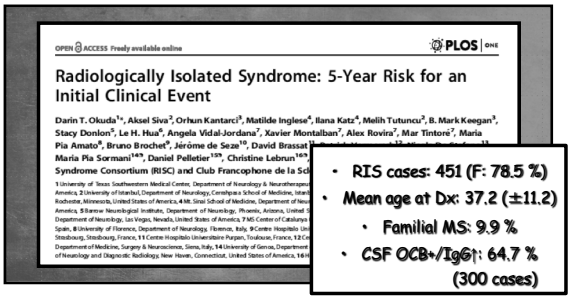
MRI anomalies not associated with any functional impairment

MRI anomalies in the CNS not better accounted for by another disease process

MRI criteria for RIS Q - should it be updated according to the recent revision of McDonald criteria?

Okuda et al. Neurology, 2009

"Radiologically Isolated Syndrome"



OPEN ACCESS Freely available online PLOS ONE

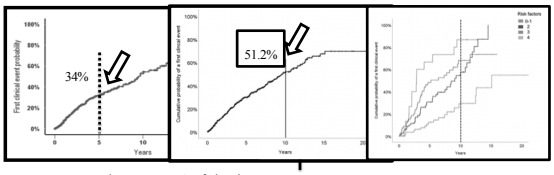
Radiologically Isolated Syndrome: 5-Year Risk for an Initial Clinical Event

Darin T. Okuda[1*], Aksel Siva[2], Orhun Kantarci[3], Matilde Inglese[4], Ilana Katz[4], Melih Tutuncu[3], B. Mark Keegan[3], Stacy Donlon[5], Le H. Hua[6], Angela Vidal-Jordana[7], Xavier Montalban[7], Alex Rovira[7], Mar Tintoré[7], Maria Pia Amato[8], Bruno Brochet[9], Jérôme de Seze[10], David Brassat[11], Maria Pia Sormani[14†], Daniel Pelletier[15†], Christine Lebrun[16†], Syndrome Consortium (RISC) and Club Francophone de la Sclé…

1 University of Texas Southwestern Medical Center, Department of Neurology & Neurotherapeu… America, 2 University of Istanbul, Department of Neurology, Cerrahpasa School of Medicine, Istanb… Rochester, Minnesota, United States of America, 4 Mt. Sinai School of Medicine, Department of Neu… America, 5 Barrow Neurological Institute, Department of Neurology, Phoenix, Arizona, United S… Department of Neurology, Las Vegas, Nevada, United States of America, 7 MS Center of Catalunya… Spain, 8 University of Florence, Department of Neurology, Florence, Italy, 9 Centre Hospitalo Uni… Strasbourg, Strasbourg, France, 11 Centre Hospitalo Universitaire Purpan, Toulouse, France, 12 C… Department of Medicine, Surgery & Neurosciences, Siena, Italy, 14 University of Genoa, Department… of Neurology and Diagnostic Radiology, New Haven, Connecticut, United States of America, 16 I…

- RIS cases: 451 (F: 78.5 %)
- Mean age at Dx: 37.2 (±11.2)
- Familial MS: 9.9 %
- CSF OCB+/IgG↑: 64.7 % (300 cases)

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

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

*Okuda et al, PLoS One, 2014 & Lebrun et al presented at ECTRIMS 2019

"Radiologically **Isolated Syndrome**"

Novel imaging techniques as biomarkers of neuroinflammation and neuroregeneration

and

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…

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 MTr was milder in RIS than in RRMS / Lesional-MTr lower in RRMS than in RIS / NAWM-MTr and cortical-MTr similar 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!**

Not all RIS are early MS

All RIS may not be the same!!!

*De Stefano et al. PLoS ONE, 2011; **Stromillo et al. Neurology 2013 & Okuda & Vernken. Neurology 2013

RIS – how early the disease process starts? …and what that does mean?

Cortical lesions (CLs) were found in 40% of asymptomatic subjects

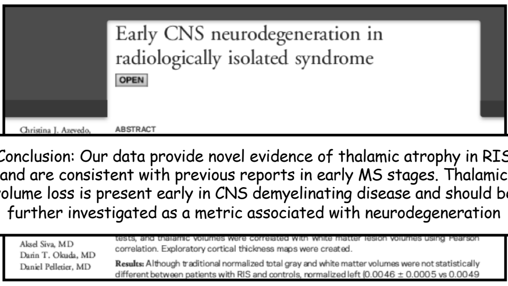
CLs were not related to more pronounced cortical atrophy or worse cognitive performance

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

"Radiologically Isolated Syndrome" Evidence for early neurodegeneration!


Early CNS neurodegeneration in radiologically isolated syndrome

OPEN

Christina J. Azevedo, Aksel Siva, MD, Darin T. Okuda, MD, Daniel Pelletier, MD

ABSTRACT

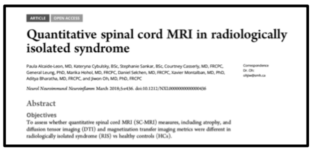
tests, and thalamic volumes were correlated with white matter lesion volumes using Pearson correlation. Exploratory cortical thickness maps were created.

Results: Although traditional normalized total gray and white matter volumes were not statistically different between patients with RIS and controls, normalized left (0.0046 ± 0.0005 vs 0.0049

Conclusion: Our data provide novel evidence of thalamic atrophy in RIS and are consistent with previous reports in early MS stages. Thalamic volume loss is present early in CNS demyelinating disease and should be further investigated as a metric associated with neurodegeneration

Azevedo et al, Neurology 2015

"Radiologically Isolated Syndrome" Evidence for early neurodegeneration!


Quantitative spinal cord MRI in radiologically isolated syndrome

Abstract

Objectives

This study found minimal micro-structural differences in the SC of RIS, despite most participants having visible lesions and no evidence of SC atrophy. MTR was lower in RIS, suggesting that inflammation and demyelination may be one of the only microstructural changes detectable in the very earliest stage of MS, which is in keeping with known pathologic mechanisms in MS

Conclusion

The SC demonstrates minimal microstructural changes suggestive of demyelination and inflammation in RIS. These findings are in contrast to established MS and raise the possibility that the SC may play an important role in triggering clinical symptomatology in MS. Prospective follow-up of this cohort will provide additional insights into the role the SC plays in the complex sequence of events related to MS disease initiation and progression.

Some structural changes but no atrophy!

Alcaide-Leon et al. Neurol Neuroimmunol Neuroinflamm, 2018

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, 2011 ECTRIMS

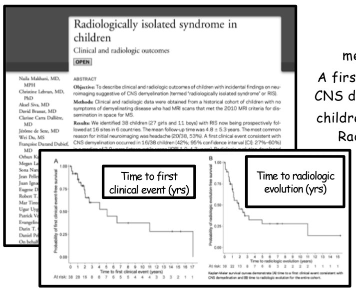
Are all PPMS are primary progressive? Does RIS may present clinically as PPMS?*

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 findings further suggest that RIS is biologically part of the MS spectrum

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

Radiologically isolated syndrome in children*


Radiologically isolated syndrome in children

Clinical and radiologic outcomes

OPEN

ABSTRACT

Objective: To describe clinical and radiologic outcomes of children with incidental findings on neuroimaging suggestive of CNS demyelination (termed "radiologically isolated syndrome" or RIS).

Methods: Clinical and radiologic data were obtained from a historical cohort of children with no symptoms of demyelinating disease who had MRI scans that met the 2010 MRI criteria for dissemination in space for MS.

Results: We identified 38 children (27 girls and 11 boys) with RIS now being prospectively followed at 16 sites in 6 countries. The mean follow-up time was 4.8 ± 5.3 years. The most common reason for initial neuroimaging was headache (20/38, 53%). A first clinical event consistent with CNS demyelination occurred in 16/38 children (42%; 95% confidence interval [CI]: 27%–60%)

38 children with RIS
(16 cites/6 countries)
mean f/up 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

*Makhani et al, Neurol Neuroimmunol Neuroinflamm 2017

"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 sydrome" who present with cognitive dysfunction?

*Hakiki et al. Euro J Neurol, 2008; **Lebrun et al, Multiple Sclerosis 2010; Amato et al, Neurology, 2011

"RIS" and cognitive involvement! What to think of it?

- Are individuals with RIS, who are found to have a similar cognitive profile with MS patients are 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 may remain subclinical unless explored with special technics 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*

*Siva A. Asymptomatic MS. Clinical Neurol Neurosurg, 2014

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 1950-95 that underwent conscription examination at ages 18-19 to the Norwegian MS registry to identify those later developing MS, and randomly selected contr
  - Men deve
    examinat
    correspo
  - Those de
    controls
- An Argentine
  cognitive dec
- However, in a
  significant difference was observed…***

Cognitive problems
may be present in all MS phenotypes
before apparent clinical symptoms develop
- RRMS may start years prior to clinical presentation and disease processes
- PPMS could start decades prior to first apparent clinically detectable progressive symptoms

*Cortese et al. Ann Neurol, 2017; **Sinay et al. MSJ, 2014; *** Gunnarsson et al. Europ Neurol 2015

The MS prodrome - Does it exist?

More frequent use of health care (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**

These observations are indicative that people with MS are likely to have non MS-specific health related problems in the years before they develop clinical MS! Suggestive that an "MS prodrome" may exist at least for some MS patients

* Winjand et al. Lancet Neurol, 2017; **Berger et al. MSJ 2013 & Byatt et al. J Neuropsyc Clin Neurosci 2011

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 sNfL levels
from a median level of 25 pg/ml to 45.1 pg/ml ***

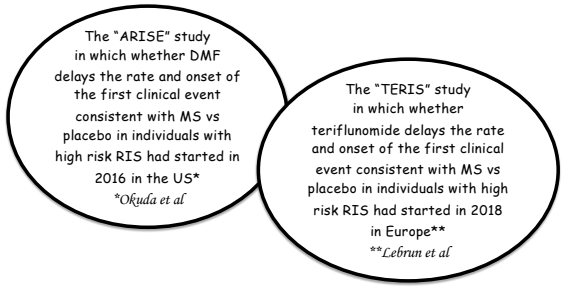
*Thouvenot et al MSJ 2018 & 2019; **Matute-Bianch et al Brain 2018;
*** Bjornevik et al. JAMA Neurology, 2019

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!

*DeStefano & Siva. MSJ 2013 & Granberg et al. MSJ 2013; **Okuda et al. PLoS One, 2014

Radiologically Isolated Syndromes



*DeStefano & Siva. MSJ 2013 & Granberg et al. MSJ 2013; **Okuda et al. PLoS One, 2014

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