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ORIGINAL RESEARCH

A Prospective Study of Patients with Brain MRI Showing Incidental T2 Hyperintensities Addressed as Multiple Sclerosis: a Lot of Work to do Before Treating

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ABSTRACT

Introduction: With the development of magnetic resonance imaging (MRI) and publications about radiologically isolated syndrome (RIS), a lot of patients are referred to multiple sclerosis (MS) tertiary centers to confirm diagnosis of RIS or MS when brain T2 abnormalities are identified, whatever their characteristics. We evaluate prospectively the occurrence of RIS or MS and sensitivity, specificity and predictive value of McDonald criteria in diagnosis for patients presenting with incidental brain MRI T2 lesions.

Methods: The authors ran standardized procedures on 220 consecutive patients addressed by general practitioners or neurologists to confirm RIS or MS diagnosis on brain MRI and give a therapeutic advice. All patients underwent neurological tests, extensive blood screening, cerebrospinal fluid (CSF) examination, visual evoked potential (VEP) and follow-up MRI after 3, 6, 12 and 24 months to consider dissemination in time and space.

Results: Patient characteristics were: 165 women and 55 men, mean age: 42.7 years old (23–59). The major symptom motivating MRI was headaches (39%), sensitive atypical manifestations or pain (12%), mood disorders (10%), transient visual symptoms (9%), fatigue (8%), hormonal screening (6%), vertigo (6%), cranial trauma (5%), and dummy run for clinical study (5%). After a structured analysis of T2 lesions, the suspected diagnosis was: inflammatory disease 45%, vascular 33%, non-pathological 19%, genetic 2%, and metabolic 1%. Extensive screening confirmed the proposed diagnosis in 97% of cases. Among all the 220 proposed RIS patients, only 35.4% fulfilled the 2010 McDonald criteria, and 8% can be categorized as RIS. Dissemination in time criteria was present for 82.7% of MS patients and 36% of RIS patients but none of the vascular or non-pathological T2 abnormalities.

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Conclusion: Even if RIS was initially suspected on MRI, only a third of the patients had an inflammatory disease. Most of the patients had either non-specific T2 lesions or a non-inflammatory disease. Others were initially well categorized but had experienced clinical symptoms that could possibly be considered as a first clinical event. Overdiagnosis of MS can lead to propose an inappropriate disease-modifying therapy.

Keywords: Brain MRI; Clinically isolated syndrome; Incidentaloma; Multiple sclerosis; Neurology; Radiologically isolated syndrome T2 hypersignals

INTRODUCTION

With the development of magnetic resonance imaging (MRI), a lot of patients are addressed to neurologists to confirm diagnosis of multiple sclerosis (MS) when brain T2 abnormalities are found, whatever their characteristics, even if white matter abnormalities are non-specific. Most of the time, the patient is presented with a radiological report notifying clearly the diagnosis of MS. A lot of non-specialized radiologists are not specifically aware of the clinico-radiological diagnosis leading to MS diagnosis. Diagnosis of MS is based on demonstrating dissemination in space (DS) and time on MRI and excluding other neurological disorders that can clinically and radiologically mimic MS [1]. The brain MRI motive has to be a seminal event, acute or progressive, suggestive of an inflammatory disease. When the patient suffers from suggestive MS symptoms, clinico-radiological criteria are helpful to diagnose a clinically isolated syndrome. McDonald criteria have been applied in clinical practice with good specificity for MRI criteria with two updates since the original publication but may require systematic screening (visual evoked potential, blood and cerebrospinal fluid analysis) [1–6]. Other criteria for diagnosis of MS have been recently proposed but are not yet validated [7]. Eventually, a lot of patients diagnosed with potential MS are not diagnosed after a second screening [8, 9].

For patients with non-typical MS symptoms, a systematic review of brain and spinal MRI is the major step to establish the diagnosis of a demyelinating disease. Recognition of MRI red flags, as defined by the European MAGNIMS (Magnetic Resonance Network in Multiple Sclerosis), improves diagnostic accuracy [10, 11].

The limited specificity of incidental non-specific white matter abnormalities that are revealed by MRI may increase the number of misdiagnosis [10]. Even prior to the introduction of radiologically isolated syndrome (RIS) criteria, longitudinal clinical data from individuals with incidentally identified T2 lesions suggestive of multiple sclerosis (MS) were described. Healthy individuals who do not exhibit signs of neurological dysfunction commonly have brain MRI studies performed for a reason other than an evaluation for MS that reveals unexpected anomalies highly suggestive of demyelinating plaques given their size, location, and morphology. These healthy subjects lack symptomatology suggestive of MS and fulfill formal criteria for RIS, a recently described MS subtype that expands upon the phenotype of at-risk individuals for future demyelinating events. A formal description of RIS was first introduced in 2009 by Okuda et al. [12], to define this relevant cohort of individuals who are at risk for future demyelinating events.

The authors describe here a prospective study consisting of the evaluation in clinical practice of a step-by-step procedure in patients presenting with non-specific symptoms and brain T2 hyperintensities, initially diagnosed as RIS or MS.

METHODS

From 2009 to 2012, the authors ran standardized procedures on 220 consecutive patients referred to their MS center by general practitioners (GP) or neurologists for specialized advice concerning suspected MS on brain MRI. Brain MRI was performed by the GP for non-specific symptoms (such as headaches, atypical sensitive symptoms, blurred vision, and mood disorders).

Classification of the T2 Hyperintensities

Clinical and neurological data were reviewed with the patient and the brain MRI was analyzed by two physicians (neuroradiologists: LM, SC or 3 neurologists: CL, AC, MC) with a standardized procedure considering shape, size, number and location of T2 and T1 abnormalities on sequences with and without gadolinium (Fig. 1). Potential chronic inflammatory disease was retained if brain T2 hypersignals were >3 mm, ovoid and then, Barkhof and Tintore criteria were applied [2]. If more than 3 criteria were present, RIS or MS was suspected and DS was documented. If hyperintensities were suggestive but with >3 DS criteria, inflammatory disease involving central nervous system was suspected.

After this first step, the patients were categorized by the neurologist into a disease group with data suggestive or not of an inflammatory process. If not, another diagnosis was proposed: ischemic vascular disease, metabolic, genetic or non-pathological. Because patients were initially assessed for a radiological suspicion of MS, all available MRI criteria applicable were applied, irrespective of what the neurologist's suspected diagnosis was [2, 4, 7, 13, 14].

Extensive Screening to Confirm the No Better Explanation Concept

As they want to have an answer for their diagnosis, all patients asked and agreed to undergo neurological tests, and extensive blood screening, including a complete blood count, erythrocyte sedimentation rate, serum cryoglobulins, total serum gamma globulins, serum protein immunoelectrophoresis, C-reactive protein, complement factors, angiotensin conversion enzyme, antinuclear antibodies, antinative DNA, antiphospholipid/anticardiolipin antibodies, rheumatoid factor, antiprothrombinase, HIV, herpes simplex virus, varicella-zoster virus, hepatitis C and B, syphilis, cytomegalovirus, and Epstein–Barr virus serological tests. All patients had a cerebrospinal fluid (CSF) analysis with cell count, protein level and an oligoclonal band (OCB) evaluation by isoelectrofocusing method. Detection of an OCB was considered as positive if more than 1 band that was not detected in the serum was present in the CSF.

At recruitment, patients had a VEP and a follow-up brain MRI was programmed with and without gadolinium at 3, 6 and 12 months to consider dissemination in time (DT) and DS. The MRI follow-up was standardized with Axial T1 3D: TE = 1.7; TR = 7.9; NEX = 2; FOV: 260 × 195 mm; 1.6 mm with 0.8 mm overlap; 256 x 192; 152 slices; Axial T2/DP (FSE double écho): TR = 5,000; TE = 8.0 et TE = 103.9; NEX = 2; FOV: 240 × 180 mm; 2.0 mm;

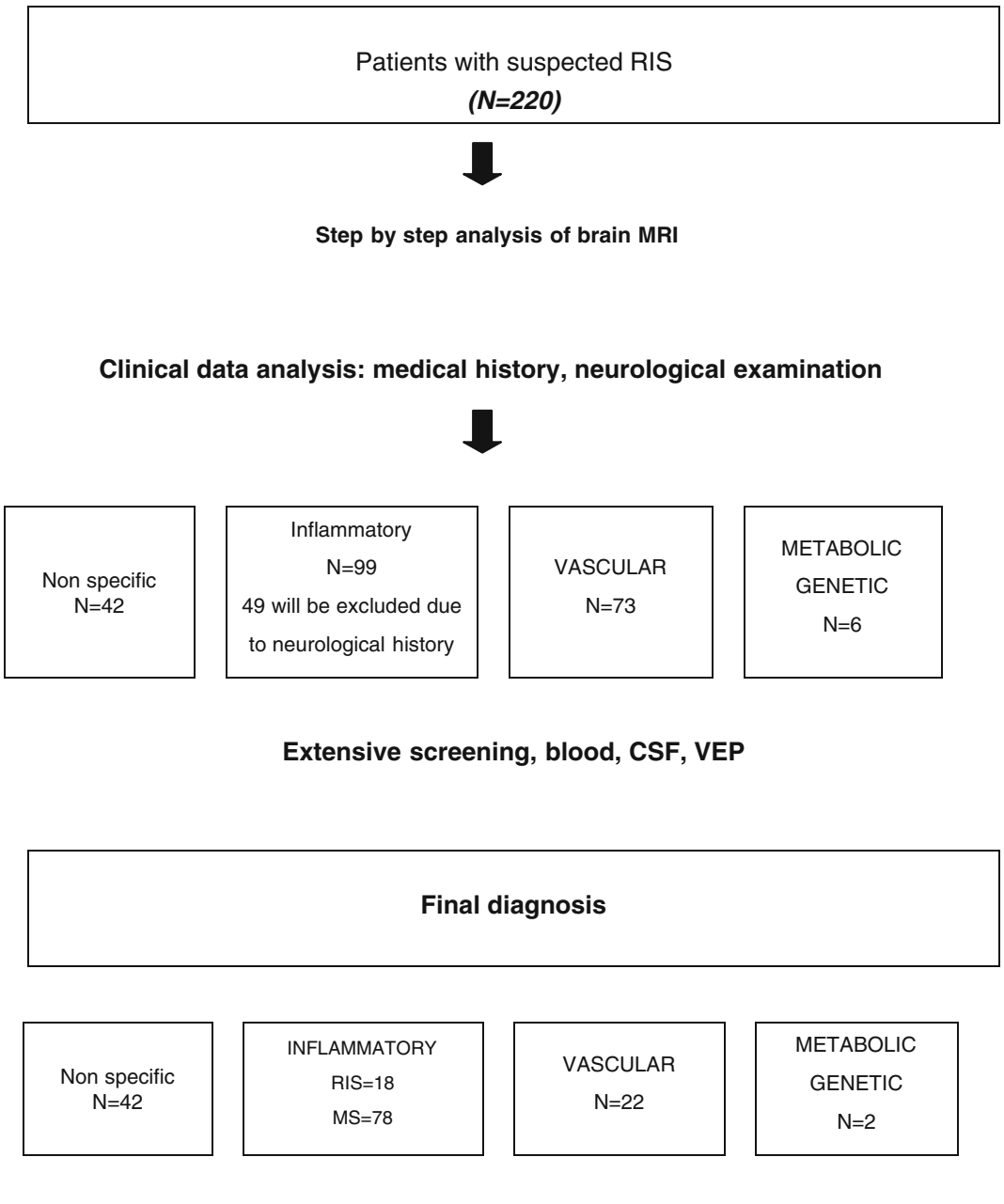

Fig. 1 Methodical process of files from radiologically isolated syndrome suspected patients

256 × 192; 64 slices; Axial Flair (FSE IR): TE = 157.5; TR = 10004; TI = 2,200; NEX = 1; FOV: 240 × 240 mm; 4.0 mm; 256 × 192; 28 slices; Gadolinium injection 0.1 ml/kg; Axial T1 post-Gd (FSE-XL): TR = 480; TE = 7.3; NEX = 4; FOV: 240 × 180 mm; 2.0 mm; 256 × 192; 64 slices.

All charts were reviewed at 2 years to confirm the final diagnosis, if possible.

Diagnosis Proposal and Follow-up

After a review of the patients' personal history, if symptoms suggestive of an inflammatory

disease were found independently of the present MRI motive and MRI criteria of DS and DT were fulfilled, the patient was diagnosed with MS. Patients with possible RIS according to DS criteria but with a history of clinical symptom compatible with a first clinical event were classified as clinically isolated syndrome (CIS).

For the other recruited patients with non-specific symptoms, a diagnosis was finally proposed on the combination of clinical, laboratory and radiological data.

Compliance with Ethics

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 and 2008. Informed consent was not required because all screenings were included in the standard clinical practice. The analysis in this article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

RESULTS

Patient characteristics were: 165 women and 55 men, mean age: 42.7 years old (23–59). Patients were categorized as to whether they had symptoms and signs possibly related to T2 hypersignals (paraesthesia, vertigo, gait control), or unlikely to be specifically related to demyelination (isolated fatigue, headaches, trauma, endocrinopathy). After an extensive discussion, typical symptoms of demyelination, either optic neuritis or myelitis, evoking a CIS were found in 22% of patients with T2 hypersignals suggestive of RIS. These symptoms were not the MRI motive but the patient was then excluded.

Table 1 Repartition of suspected radiologically isolated syndrome patients

MRI motive	N (%)	Clinical history (%)
Headaches	87 (39)	2
Atypical Sensitive symptoms	26 (12)	15
Mood disorders	22 (10)	3
Visual	20 (9)	11
Fatigue	17 (8)	1
Hormonal screening	13 (6)	2
Vertigo	13 (6)	2
Trauma	11 (5)	1.5
Dummy run	11 (5)	1.5

The major symptom motivating brain MRI was headaches (39%), sensitive atypical manifestations (12%), mood disorders (10%), transient visual symptoms (9%), fatigue (8%), hormonal screening (6%), vertigo (6%), cranial trauma (5%), dummy run for clinical study (5%) (Table 1).

After a structured analysis of T2 hyperintensities, the suspected diagnosis was: inflammatory 45%, vascular 33%, non-pathological 19%, genetic 2%, and metabolic 1%. Extensive screening confirmed the proposed diagnosis in 97% of cases. From the 6- and 12-month visits, diagnosis was confirmed and only three cases remained unresolved. Among the 220 patients, only 78 (35.4%) fulfilled the 2010 McDonald criteria, and 18 (8%) were categorized as RIS (Table 2).

DS with MS/MRI criteria applied to the first brain MRI were fulfilled in 85% of MS, for 34.6% of the vascular patients, and for 0 of the non-specific hyperT2 (Table 3). 38% of patients

Table 2 Comparison between the suspected and final diagnosis

Suspected diagnosis	N (%)	Relevant Clinical history	Final diagnosis
Inflammatory	99 (45%)	49 (22%)	RIS. 18 (8%)
			MS. 78 (35%)
			Other inflammatory diseases. 4 (2%)
Vasculopathy	73 (33%)	22 (10%)	37 (17%)
Non-pathological	42 (19%)	–	68 (31%)
Genetic or metabolic	6 (3%)	4 (2%)	2 (1%)

9 (4%) patients had unexplained T2 abnormalities after 2 years of follow-up
MS multiple sclerosis, *RIS* radiologically isolated syndrome

underwent initial spinal MRI. Among those who had T2 hyper intensities compatible with MS, 33% of them had spinal T2 lesions.

Regarding the patients who had a final diagnosis of demyelinating disease, all MS/MRI criteria have the same sensibility (Table 2) [2, 13]. The association of 2 DS criteria, a positive CSF and DT on MRI was also sensitive and specific. None of the patients with vascular diseases or non-pathological T2 hypersignals had MRI criteria and a positive CSF. DT criteria were present for 82.7% of MS patients and 36% of RIS patients but none of the vascular or non-pathological T2 abnormalities.

At 6 months, 35.4% of patients had finally been diagnosed as inflammatory disease with DT and DS. On the 24-month visit, diagnosis was confirmed and only three cases remained unresolved. For cases other than RIS or MS, diagnosis was confirmed with the paraclinical screening and identification of risk factors such as cardiovascular risks, metabolic abnormalities, and genetic diagnosis (one case of fragile X-associated tremor/ataxia syndrome). The 2-year diagnostic distribution was: RIS 8%, MS 35%, other inflammatory diseases 2%, ischemic vascular disease 17%, non-pathological 31%, genetic 1%, and unknown 4%.

DISCUSSION

Brain MRI is the most sensitive paraclinical diagnostic test for MS, but white matter abnormalities are also known to be present in many other circumstances [1, 14–16]. They have been reported in 40–95% of patients with other neurological diseases [8–10] and even in 44% of elderly asymptomatic patients [13]. Failure to consider the aspect of T2 hypersignals can induce misdiagnosis in some patients fulfilling the criteria of DT and DS. In these cases, proposing specific treatments that are available now can be risky.

Among our 220 suspected MS patients, 43% were diagnosed with demyelinating disease and 22% with clinical MS, due to history of symptoms suggestive of a clinical event, acute or progressive. With an extensive questionnaire, neurologists can detect previous neurological event that patients failed to report. This contrasts with another study where 11% of 104 patients had suspected MS based on MRI [17]. Recently, the PEDIAS study revealed that 44% of patients with a typical CIS had a neurological history suggestive of a previous demyelinating event [18].

Other published studies showed that in the vast majority of patients who were referred with

Table 3 Data (% of patients) on fulfilled MRI criteria according to the final diagnosis

MRI criteria (%)	MS (%)	Other inflammatory diseases (connectivitis) (%)	Vasculopathy (%)	RIS (%)	Non-pathological (%)
3 DS criteria BARKHOF	**85**	**20**	34.6	100	0
PATY	90	50	72.3	71.4	33.3
FAZEKAS	90	20	3.9	14.3	0
SWANTON	90	40	42.3	88.6	6.7
Non-specific T2 hypersignals	**5**	**0**	7.7	28.6	86.7
2 DS criteria + CSF abnormalities	57.8	30	0	42.3	0
DT MRI only (new T2 or gadolinium +)	**82.7**	0	0	36	0
Association of 2 HS + CSF and DT on MRI	**90**	30	**0**	44	**0**

DS dissemination in space, *DT* dissemination in time, *HS* hypersignal, *MS* relapsing remitting multiple sclerosis, *CSF* cerebrospinal spinal fluid

suspected demyelinating disease, but in whom no diagnosis could be made at the time of referral, no neurological diagnosis was made during an average follow-up of 7 years [8, 9]. Finally, diagnostic uncertainty remains for a significant number of patients. For instance, the manifestations of a patient with non-specific, multifocal symptoms not typical of a CIS may still be wrongly diagnosed as possible MS. Correspondingly, potentially confirmatory MRI and other test results may be normal or nonspecifically abnormal. In these cases, definite diagnosis is not possible and follow-up is required.

In our cohort, the majority of T2 lesions diagnosed on MRI as possible MS were non-specific lesions. The medical history and clinical analyses in MS diagnosis are very important [19]. In most patients in whom ultimately another diagnosis was made, it was found that at initial clinical presentation a diagnosis of MS could be rejected based on the association of medical history and MRI findings. Specific symptoms or signs pointing to the disease were not recognized.

With the extending accessibility of MRI, RIS is frequently overdiagnosed, either because medical history examination reveals a suggestive clinical event or the structured MRI analysis rejects the diagnosis of an inflammatory disease. Among our 220 patients, only 18 were finally diagnosed as RIS, others having either neurological symptoms history or T2 lesions nonsuggestive of MS. Even if incidental brain T2 lesions are frequent, asymptomatic patients with hypersignals and/or gadolinium enhancement fulfilling Barkhof/Tintoré MRI criteria and DT and DS are more rare [12, 20–24]. DT criteria were present for 82.7% of MS patients and 36% of RIS patients but none of the vascular or non-pathological T2 abnormalities.

In these published cohorts, 80% of patients with a RIS already fulfilled diagnostic criteria before the seminal event. In European or North American observational studies, the authors have found that up to 30–45% of patients with RIS will present clinical progression. [12, 21] The median time to clinical conversion differs between studies being 2.3 years for the series of French patients and 5.4 years for the American. Most patients who develop clinical symptoms had prior radiological progression. The presence of asymptomatic lesions in the

cervical cord provides an increased risk of progression, either to relapsing or to progressive MS.

In longitudinal studies, it has been shown that 88% of patients with brain T2 abnormalities developed MS and even if new lesions can be clinically silent, the ratio of MRI activity to clinical relapse is approximately 7–10% [4, 6, 15]. Nevertheless, before the clinical threshold, other inflammatory diseases might always be suspected. Many inflammatory or infectious disorders (e.g., systemic lupus erythematosus, sarcoidosis and neuroborreliosis) that are commonly part of the differential diagnosis can be investigated by blood and CSF analyses [10]. Patients with migraine are also frequently diagnosed with T2 abnormalities and may be over diagnosed as RIS [25–27].

When applied intentionally, MRI and McDonald criteria are very specific and sensitive, providing their application is limited to MRI abnormalities suggestive of MS, after exclusion of 'red flags'. In this study's cohort, there were neither false positives nor false negatives for other pathologies than MS.

The paraclinical screening, for which there is no international consensus in the literature, is not mandatory for diagnosis of MS. Nevertheless, it can be very useful to diagnose DS or exclude other diagnoses [28–31]. Even if this population is clearly different from that seen in general neurological clinics and is biased towards diagnostic uncertainty, a lot of investigations could be spared if the diagnostic criteria are correctly applied.

CONCLUSION

Patients and their physicians could be more at ease if radiological reports were not so affirmative concerning the MS diagnosis without considering the clinical aspects. Nevertheless, some tests are suggestive of a CNS inflammatory disease, reinforcing diagnosis and bringing in another element for prognosis, thereby guiding treatment. Given the benefits of early treatment in MS, but also their further implications, diagnosis as soon as possible is certainly essential.

Despite advancements in the characterization of RIS subjects and in the understanding of risk factors for initial symptom development, the natural course of such cases and risk profiles for a seminal neurological event, from prospectively acquired data, remain unclear.

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Conflicts of interest. Christine Lebrun received honoraria for scientific boards from Bayer, Novartis, Teva, Almirall, Merck, Biogen Idec, Genzyme. Mikael Cohen received honoraria for scientific boards from Bayer, Novartis, Teva, Genzyme, Merck, Biogen Idec. Annabelle Chaussenot, Lydiane Mondot and Stephane Chanalet have no conflict of interest to declare.

Ethical standard. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as

revised in 2000 and 2008. Informed consent was not required because all screenings were included in the standard clinical practice. The analysis in this article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

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