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CLINICAL, IMAGING AND, THERAPEUTIC FEATURES OF MULTIPLE SCLEROSIS IN CHILDREN

DOCTORAL THESIS SUMMARY

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2. Dică AD, Craiu D, Iliescu C, Găină M-A, Sandu C, Pomeran C, Bârcă D, Butoianu N, Burloiu C, Minciu I, et al, *Pediatric-Onset Multiple Sclerosis (POMS) and Epilepsy: Exploring Etiological Complexity—Outcomes from a Single-Center Experience, Children,* 2025; 12(5):631. doi.org/10.3390/children12050631. https://www.mdpi.com/2227-9067/ 12/ 5/ 631 (Cap 4, pag 62-79)

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Epidemiological data

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) characterized by acute episodes (with variable neurological signs and symptoms - vision impairment, motor deficits, balance and/or sensitivity disorders, etc., called relapses or exacerbations) and periods of remission (the patient is asymptomatic) associated with demyelinating lesions (in different stages of evolution) located in the brain and/or spinal cord, primarily affecting adults aged 20-40 years. However, ~5% of cases (up to 10% according to some authors) begin in childhood (<18 years, especially between 13-16 years) and <1% at age <10 years [1-7].

Although multiple sclerosis is rare in children, and very rare at a young age (<10 years), its frequency has increased in recent years [8,9], with an incidence rate reported between 0.2-2.9 per 100,000 among individuals under 18 years old and a prevalence between 2.8-6.0/100,000, with an even wider range (0.7-26.9) depending on the country and the cohort of children evaluated [5, 6, 10-12]. Experts in the field have been driven to provide more attention to this segment of the population as more children are diagnosed.

Pediatric neurologists have always found difficulty in the variety of the initial neurological symptoms, sometimes unusual, the unpredictable clinical course, the typically distinctive imaging appearance—large, extensive lesions—and the limited treatment choices. Recent advances in the field—blood and cerebrospinal fluid biomarkers with increased sensitivity and specificity, particular traits of demyelinating lesions recently described with changes to the protocol for central nervous system imaging, and highly effective treatments that have shown positive effects on disease control in adults, with some already recently used in children and others now being tested in children under clinical trials—help in the early diagnosis and prompt start of suitable treatment, tailored to the needs of each patient.

Equally vital is the exceptional negative effect such a diagnosis has on the child or teenager and their family members, so greatly changing the quality of life for the sufferers. This highlights the need of a multidisciplinary team comprising medical professionals specializing in diagnosing and treating demyelinating diseases—pediatric neurologists, doctors from other specialties, nurses, physiotherapists—as well as non-medical personnel such as psychologists and social workers involved in their care.

Last but not least, the very small number of publications on this topic at the national level, as well as from Eastern Europe, and my special interest, since my residency years, in this fascinating, incompletely studied and understood pathology, were other factors that led me to address this subject.

The main objective of the research was to highlight the clinical, imaging, and therapeutic characteristics of multiple sclerosis in pediatric age and was conducted as *a retrospective, observational, longitudinal study* over a period of seven years within the Pediatric Neurology Clinic of the "Prof. Dr. Alexandru Obregia" Clinical Psychiatric Hospital, the largest tertiary Pediatric Neurology center in the country and until recently the only one where the National Treatment Program for Rare Diseases in children, including Multiple Sclerosis, was conducted, with over 15 years of experience.

The features of the studied cohort, especially those pertaining to modes of onset, the fast progressive course of multiple sclerosis before treatment start and with disease-modifying therapy for one to three years, and even up to five years for some children with early onset, quantified by the number of relapses per year, the new lesions on MRI, particularly the active ones, as well as the value of the EDSS score which assesses accumulated motor disability, also reflected the main goals of the study.

Although no less important, the secondary objectives evaluated the impact of risk and environmental factors on disease progression, the duration from disease onset to diagnosis, and from diagnosis to treatment initiation—in some cases, these delays were due to local "beliefs" (delayed presentation to the doctor, incomplete investigations and vaccination schedules), and limited access to some high-efficacy therapies approved for children due to legal frameworks and limited financial resources.

I think this study was absolutely required and offered useful insights on the present state of multiple sclerosis in children at the national level, the current diagnostic and treatment challenges, and the very small number—with some areas still to be explored—of specialists in the field that patients and their families can reach. This provided the background and drive for the pediatric MS working group to revise and standardize the diagnosis and treatment protocol for children, actively participate in revising the national treatment recommendations with adult neurologist colleagues, and execute the national registry to obtain precise data on the actual impact of this pathology in Romania.

The results obtained and published on the studied cohort are similar to those in the specialized literature and serve to complete the overall picture of autoimmune-inflammatory diseases at the international level.

The limitations of the research are primarily related to the small and heterogeneous number of patients studied, the use of similar but not identical protocols for performing MRIs (different centers), which prevented the study of aspects related to the size of the lesions and the clear assessment of the degree of cerebral atrophy, as well as the fact that the impact of the disease on the

cognitive side and the quality of life of the affected children and their families was not evaluated using standardized tests, representing a new direction for research.

Risk factors' significance

The most important external risk factors for the onset of MS in pediatric age are: infection with the Epstein-Barr Virus (EBV), as well as other pathogens (other herpesviruses, Covid-19), including vaccination, vitamin D3 (25(OH)D3) deficiency and exposure to sunlight, smoking, alcohol consumption, unhealthy diet, and pollution (atmospheric, household detergents, etc.) [13].

Equally important are the internal risk factors, among which are: obesity, the gut microbiome, the female gender, and sex hormones, particularly during critical times connected with hormonal change in a woman's life: puberty and pregnancy [13].

Mechanisms of demyelination and immune system involvement

The onset of multiple sclerosis is not completely recognized or understood [14, 16], several theories being accepted, that appear to interact with genetic and environmental elements in an effort to clarify the cause of MS.

The first theory is that of an immune-mediated inflammatory process through the autoactivation of lymphocytes [17], which over time affects microglia and produces chronic neurodegeneration [16]. Therefore, demyelination, inflammation, and axonal degeneration play a major role in the onset of MS [14, 15].

Pro-inflammatory cells (B, T), Th1, and macrophages [18, 19] activate inflammation, which destroys the blood-brain barrier (BBB), emphasized on MRI by the uptake of contrast agent in the periphery of active lesions from the onset of the disease [20]. This allows lymphocytes and other inflammatory cells into the CNS, where they affect myelin, oligodendrocytes, and cause axonal neurodegeneration. Thus, the peripheral immune system participates in both phases of the inflammatory process: acute—during relapses and chronic—the gradual progression of the disease at the cerebral level, but without knowing precisely how the peripheral immune cells are drawn by the intrinsic factors of the CNS to invade the cerebral parenchyma [21].

Other theories debated by specialists to understand the etiology of MS include the one through an immune effect, but not autoimmune, induced by a chronic viral infection, the most discussed variant being EBV infection. However, this is not present in all MS patients, which is why EBV infection is currently considered only an important risk factor in the onset of the disease

[17, 22], as well as genetic factors.

Genetic factors

Recent research reveals an increased genetic susceptibility among individuals with MS, which, along with environmental factors, complexly interacts with autoimmune inflammatory processes, triggering the disease among patients [23, 24].

A positive family history in ~20% of patients increases the risk 10-20 times compared to the general population (~1/1000 people) of developing MS if you have a sibling or a parent with this disease [24-26].

Particularly the HLA-DRB1*15.01 allele in the European population, HLA (Human Leucocyte Antigen) is the gene family linked to the genetic predisposition of 20-30% of individuals who develop MS, occasionally interacting with low levels of vitamin D3 [27, 28].

Over 200 unique genes have been found by means of the GWAS (Genome Wide Association Study) technique; these genes lie outside the major histocompatibility complex (MHC) including HLA and cannot cause the disease by themselves but can raise its risk. Among the most important genes are IL7R, IRF8, TNFRSF1A, CD6, etc. [29, 30].

Pediatric age peculiarities

The affectation is equal, regardless of gender (girls:boys (1:1)), before puberty, with an observed predominance of 2-4:1 of the female sex after the onset of puberty [6, 31, 32].

The age of onset is particularly crucial since the neurological signs and symptoms differ at a very young age (<10 years) compared to those with onset in adolescence (>12-13 years) [31-34]. Given that the intermediate age has characteristics from both categories, evolving from child to adolescent, and patients in this group cannot be exactly classified into either of the other two, I think patients should be divided into three groups: early onset (<10 years), intermediate age (between 10-12 years), and late onset (>12 years) [35].

Early onset (<10 years) usually indicates multifocal involvement and atypical symptoms that may confuse the pediatric neurologist during diagnosis. These symptoms clinically present as ataxia, several cranial nerve involvement, acute disseminated encephalomyelitis (ADEM-like - confusion, aphasia, balance issues, vomiting, headache), unilateral motor deficits, suggesting mostly infratentorial involvement of the CNS [31-34].

Onset in adolescence (>12-13 years) often indicates monofocal involvement, and the clinical picture at onset resembles that of adults with: unilateral motor deficit (hemiparesis or monoparesis), sensory disturbances, unilateral optic neuritis or vestibular syndrome, symptoms suggestive of supratentorial involvement [12, 31, 33, 34].

The progression of MS in children is faster, the disease manifests more aggressively [32,

36]. 95-98% of them have relapsing-remitting MS within 2-5 years of onset, particularly at a young age [12, 32, 37-40], Brain and spinal cord imaging shows more numerous, extensive, active lesions [31-34, 41-43] as well as cerebral atrophy [6].

Usually, especially after the first two, kids completely recover following the initial relapses; their deficit accumulation over time is slower than that of adults [1-3, 31, 37, 44-47]. However, in the long run, these deficiencies become clear sooner [43, 48-50].

While most of the rest get impaired over time, one-third of juvenile patients show cognitive issues in the initial months of disease progression [38, 45, 51, 52].

The clinical picture

The clinical picture at onset and, in evolution, at different ages will be briefly illustrated.

More prevalent at a young age (<10 years), *ADEM-like* is a rare beginning of MS in children that affects 8-24% of cases [53-56]. Clinically, the patient exhibits encephalopathy, a required symptom for the diagnosis of ADEM, which manifests as changed mental state (lethargy, confusion, irritability) in the absence of fever and an acute infectious background. It might be linked to: headaches, vomiting, motor impairments, balance problems, cranial nerve involvement, and occasionally seizures. Within five years of experiencing a new non-ADEM relapse at least three months following the ADEM, 17% will be diagnosed with MS [57, 58].

Common early onset of MS is *ataxic syndrome*, which is characterized by balance problems and inflammatory lesions in the cerebellum (12%) [59] or the brainstem (50.3%) [56]. Associated with intentional tremor and dysmetria in paretic tests, cerebellar involvement shows as balance problems during walking, particularly in tandem walking or when turning, and occasionally the child may even be unable to walk; speech is jerky and hurried [54-58]. Internuclear ophthalmoplegia generally reflects brainstem involvement [54]. Children might have dizziness, vomiting, and diplopia in both circumstances. Pediatric MS's emergence is predicted [60, 61].

In young age (10%), *multiple cranial nerve involvement* is a more common clinical presentation; it also affects teenagers as well, caused by inflammatory lesions at the brainstem level [54, 56]. Often, several cranial nerves (III, IV, V, VI, VII) are afflicted bilaterally; however, a single nerve may also be impacted—more frequently in teenagers. The VII (facial) and V (trigeminal) nerves are more often engaged in this situation; the patient may have peripheral facial paresis or "facial weakness", diplopia (12%), and even internuclear ophthalmoplegia (30%) [33, 59].

Unilateral/bilateral motor deficit/transverse myelitis is one of the most prevalent forms of onset at all ages (3-22/50%), adolescents>children, generally unilateral in the form of hemi-/monoparesis or asymmetrically bilateral in the case of transverse myelitis. It can arise abruptly or subacutely (4 hours - 21 days) [53-55, 59]. While the sudden onset of impairment is more

suggestive of another pathology [53, 62-64], myelitis in women and the usual imaging look of the spinal cord point to MS.

The lesion can be cerebral but notably spinal in transverse myelitis, with involvement of the pyramidal pathways linked with sensory problems and level of impairment, occasionally with sphincter disturbances for urine or feces [54, 62, 63].

Present in both older and younger children in a percentage of 22-36%, often bilateral (more often in younger children), but also unilateral, *optic neuritis* ranks among the most frequent modalities of beginning or relapse of MS [7, 53-55, 62]. Clinically, it is shown by different degrees of visual acuity loss, eye movement pain or retroocular discomfort, central scotoma, visual field disturbance, and color perception problems (dyschromatopsia), acute or subacute onset [54, 55, 63]. A brain MRI using an optic nerve sequence can show hyperintensity with contrast enhancement at the level of the damaged optic nerve. Typical brain MRI and the finding of oligoclonal bands in CSF fluid are more suggestive of MS [66].

Sensory disturbances—sensory impairment mainly at an older age with 28.2-47% of cases starting this way, sometimes linked with motor deficits, other times independent, usually developing subacutely, progressively, affecting only certain types of sensitivity or all components, described as paresthesias, sometimes painful [55, 57, 59, 64].

Types of MS

Common in children, the first two kinds are clinically isolated syndrome (CIS) and relapsing-remitting forms (RRMS); secondary progressive (SPMS) and primary progressive (PPMS) follow.

Isolated clinical syndrome (CIS) is the first demyelinating event with clinical signs suggestive of MS, lasting at least 24 hours, with an acute or subacute onset, in the absence of a personal history of demyelinating disease, without association of encephalopathy or infection, in which the initial MRI appearance may or may not be suggestive of MS [53-57, 62].

Therefore, the diagnosis of MS can be made if the patient has an episode with neurological indications indicative of MS and the MRI abnormalities satisfy the McDonald 2017 criteria for dissemination in time and space (this applies to children aged > 11 years) [2].

The diagnosis of MS could be made if the patient presents during the episode with clinical symptoms explained by 2 demyelinating lesions in 2 of the usual areas for MS on MRI (periventricular, cortical or juxtacortical, infratentorial, medullary, except for the optic nerve lesion in optic neuritis) and positive oligoclonal bands in CSF [2].

In the case of probable MS (about 80% progress to MS), the patient has a multifocal episode, at least two clinical signs, and at least one symptomatic lesion on MRI, which calls for the criterion of dissemination in time OR if there are monofocal symptoms during the episode and at

least one symptomatic lesion on MRI, which calls for criteria of dissemination in time (DIT) and space (DIS). Only 15% of patients will be later identified as MS if we have mono- or multifocal clinical symptoms at initiation and negative MRI [2, 55-57].

Of pediatric MS patients, 97-98% have the Relapsing-Remitting form (with relapses and remissions); the second exacerbation typically occurs within the next two years from the first one—for example, in 36% of cases, this occurs if the onset of the disease is with an episode of optic neuritis [39, 55, 67].

In the absence of an intercurrent infection, relapses are the emergence of new acute neurological symptoms lasting more than 24 hours; most often, the clinical symptoms remit after treatment of the acute exacerbation, sometimes even spontaneously, in the early stages (the first 2 years), with an increased frequency and severity (53%) of relapses. Across age groups—children and teenagers—no change was seen in these features [53-55, 62].

Radiologically isolated syndrome (RIS) is an incidental finding of typical demyelinating lesions in asymptomatic patients who underwent a brain MRI for other complaints, without a history of neurological episodes within an autoimmune-inflammatory illness [68, 69].

Usually with the relapsing-remitting kind, about one-third of RIS patients may eventually develop MS in the next five years [70].

Among the uncommon types of MS, with tumefactive, broad, concentric lesions, we highlight the Balo form that manifests in children and young adults, where the lesions are enormous (>2 cm, even >3 cm), with a mass effect, acting like a tumor. Study I [71-74] will address this form.

Paraclinical investigations

MRI plays an essential role in MS, both in adults and children. In the case of a patient with acutely/subacutely onset neurological symptoms, it is mandatory to perform imaging investigations such as a 1.5T brain or spinal cord MRI, with contrast if changes are observed [75]. It is an investigation used for diagnosis, monitoring disease progression, and evaluating treatment response [76]. The mandatory sequences are: axial and sagittal T2, T1, FLAIR, DWI, pre- and post-contrast, and optional but recommended 3DT1 (brain volume), DTI (axonal damage), SWI (central vein sign), DIR (posterior fossa, spinal, cortical lesions) and for the optic nerve T2 with fat suppression axial and coronal or STIR, with fine sequences, under 3 mm [74].

Usually found in the white matter, small (<1 cm), ovoid, with obvious, well-defined borders, appearing homogeneously hyperintense on T2, cerebral lesions in pediatric MS seem larger owing to severe perilesional edema in children and have a tendency to confluence. Typical sites are spinal, infratentorial (children 61%), juxtacortical (U-fibres), and periventricular (86%). With a sensitivity of 95% and a specificity of 88% for the emergence of MS, black holes are ancient lesions,

hypointense on T1, produced by a very severe demyelination process and axonal loss [75-77].

Those specific blood tests are for distinguishing from other demyelinating disorders (particularly neuromyelitis optica - NMOSD and MOG-associated diseases - MOGAD) or infectious causes. Thus, the following will be determined: anti-AQP4 antibodies (NMOSD), anti-MOG (MOGAD), anti-dsDNA (SLE), anti-TPO (thyroiditis), IgM and IgG Borrelia (b Lyme) - which should be negative, EBV (can be +), vitamin D3 levels (frequently low), as well as newer neurodegeneration markers such as neurofilaments light chains (NFL) used both as predictors for the onset of MS and in monitoring disease activity (they increase before relapses) [78-80, 81-84, 85, 86].

Oligoclonal bands (OCB), which are linked to the onset of MS if the markers for other demyelinating conditions are negative and are a diagnostic criteria according to the McDonald 2017 criteria [88], represent the particular analyses from CSF. Though not particular to MS and can appear in other inflammatory pathologies, OCB are not unique to MS. Initially derived from CSF, NFL values mirror those in serum, hence establishing the diagnosis of MS [85, 86]. Cheaper and simpler to assess than BO, free light chains kappa (k-FLC) are neuroinflammation indicators with diagnostic accuracy comparable to BO and prognostic value for early MS activity [87].

Visual evoked potentials (VEP) and optical coherence tomography (OCT) are other required and beneficial studies, particularly if the patient has NO.

VEP, a non-invasive, sensitive test, shows the delay in axonal conduction or even its absence in demyelination regions, hence functioning as a negative prognostic indicator and a tool for monitoring MS patients [89]. OCT is a non-invasive technique for measuring the macular cells as well as the thickness of the retinal nerve fiber layer (RNFL). A biomarker for disease progression, the decrease of RNFL and macular cells directly corresponds with fresh brain lesions and the aggravation of brain atrophy [90].

Positive diagnosis

Associating episodic clinical symptoms with certain imaging alterations in the shape of the updated 2017 McDonald criteria from the table below [2, 91] establishes it.

Clinical manifestations	Number of lesions on MRI + clinical signs corresponding to the lesions	Additional data needed for MS diagnosis		SM Diagnosis
		Dissemination in space (DIS)	Dissemination over time (DIT)	
≥2 attacks	≥ 2 lesions + associated clinical signs	NO	NO	YES

≥ 2 attacks	**1 lesion + associated clinical signs + previous history of clinical episode with signs of involvement** *in a different region than the one currently affected*	**NO**	**NO**	**YES**
≥ 2 attacks	**1 lesion + associated clinical signs**	**+ DIS necessary**	**NO**	**YES**
1 attack	**≥ 2 lesions + associated clinical signs**	**NO**	**+ DIT necessary**	**YES**
1 attack	**1 lesion + associated clinical signs**	**+ DIS necessary**	**+ DIT necessary**	**YES**
Typical CIS	**2 leziuni + semne clinice coresp (DIS)**	**NO**	**OCB + in CSF (DIT)**	**YES**

DIS (dissemination in space) means a new attack with evidence of affecting another level of the CNS **OR** an MRI with a T2 hyperintense lesion typical of MS in 2 out of the 4 CNS areas, excluding the NO lesion.

DIT (dissemination in time) = a new clinical attack **OR** an MRI showing the simultaneous presence of lesions with and without contrast enhancement OR a new hyperintense T2 lesion OR a contrast-enhanced lesion compared to the baseline MRI regardless of the follow-up timing OR positive oligoclonal bands in CSF.

The differential diagnosis is primarily made with other autoimmune-inflammatory conditions that "mimic" MS. Thus, it will be especially differentiated from ADEM (which was presented above in the onset manifestations), NMOSD, and MOGAD.

NMOSD is a collection of inflammatory CNS disorders defined by axonal lesions and immune-mediated demyelination, particularly at the level of the optic nerves and spinal cord [53, 62]. The particular biomarkers are IgG AQP 4 autoantibodies that bind to astrocytes, activate the complement system, and invade the tissue with leukocytes, T lymphocytes, and NK cells, causing astrocyte death, oligodendrocyte damage, and neuron impairment [92]. Clinically, it shows as NO (22-36%) [63] or MT [53], usually without postrema involvement (vomiting (38%), nausea, intractable hiccups), brainstem (oculomotor dysfunction, ataxia), or hypothalamus (narcolepsy, anorexia, diuresis impairment, hypothermia, hypersomnia) [63]. Of those, 60% had the second relapse within the first year of onset. Anti-AQP4-IgG antibodies are linked to a poorer progression, more relapses (81%\u201391%), girls are more affected, and NMO is more often linked with other autoimmune diseases (SLE, sarcoidosis, myasthenia gravis, etc.) [53, 54].

MOGAD - is a demyelinating disease that clinically manifests as: ADEM (45%), NO (29% - more severe, bilateral, does NOT affect the optic chiasm), MT (11% - severe deficit, sphincter and erectile dysfunction), association of NO+MT, or involvement of the postrema area.

Although it is often monophasic, these phenotypes can recur [93]. The biomarkers are anti-MOG antibodies that should be determined within <3 months from onset, preferably using the CBA method [94].

Both are treated immediately like MS; pulse therapy with high doses of methylprednisolone for 5 days followed by oral Medrol reduction in MOGAD very slowly over 3-4 months to avoid relapse. Chronic treatment differs from that of MS.

Diseases associated with pediatric MS - they are often autoimmune, such as type 1 diabetes or Hashimoto's thyroiditis, and in 5-10% of cases, epilepsy is also associated, which in children can have a genetic cause. Thus, in the case of children with MS and epilepsy, the etiology can be autoimmune (secondary to MS), genetic (independent of MS), or combined, with the two conditions influencing each other. This aspect will be discussed in detail in Study II [95].

MS treatment

In a relapse, treatment involves pulse therapy with Methylprednisolone 1g/day or 30mg/kg/day for 5 days, followed by Medrol orally for 2-3 weeks. In the rare situation where the response is minimal, plasmapheresis or IG 2g/kgc/course divided over 5 days can be done.

Chronic treatment with disease-modifying therapy (DMT) will be initiated as soon as possible after the diagnosis of MS is established, by and under the supervision of a pediatric neurologist specialized in multiple sclerosis, with a medication in accordance with the current guidelines, tailored to the patient's needs [10].

Currently, the first line of treatment is still represented by the old platform therapies with moderate efficacy, from the class of beta interferons (IFNb) and glatiramer acetate (GA), which are administered by intramuscular or subcutaneous injection, using the escalation method. Treatment starts with a moderately effective drug (MET) and, in the absence of a response to treatment, it advances to the higher class [10, 96-98]. This approach is also used because many of the high-efficacy therapies (HET) are not yet approved for children, being used off-label in very active forms, with many clinical studies ongoing, including in our clinic. Fingolimod (FTY) is currently the only high-efficacy therapy (HET) approved for the treatment of pediatric MS, which has proven its efficacy compared to older therapies [99-102]. Among the HETs now pending approval for children, monoclonal antibodies including natalizumab, ocrelizumab, rituximab, and alemtuzumab should be noted [103-105]. Given that IFNb has been used in our clinic since 2010 and Fingolimod (FTY) since 2022, and soon Dimethyl fumarate and Teriflunomide, recently approved in our country (November 2024), will be available, with moderate efficacy but oral administration, IFNb and FTY were thoroughly investigated in the thesis under the IV research on the efficacy and safety of the two DMTs in the studied patient cohort, emphasizing the superiority

of FTY.

IFNb - are a class of immunomodulators used in CIS and RRMS, with an EDSS score of 0 - 5.5 or in SPMS with EDSS ≤ 6.5, from the age of 12, except for Rebif which is administered from the age of 2, having a good safety profile, with adverse reactions similar to those in adults, reducing the relapse rate, but due to the injectable administration (im or sc), compliance is low, especially from the third year of administration, decreasing by 50% [96-98]. In the first months of administration, pseudo-flu symptoms may occur, frequently within the first 24 hours post-administration, irritation at the injection site, and slight increases in transaminases, most of which are transient [98, 99], without any severe adverse reactions in the 15 years of use in our clinic. However, despite correct administration, 30-40% of patients experience disease progression manifested by: ≥2 clinically confirmed relapses within 1 year, maintenance/increase in relapse rate over a period of at least 6 months, accumulation of lesions detected by imaging (≥1 new T2 lesion), or a K uptake lesion on a new MRI evaluation compared to the one prior to medication [106, 107].

FTY - is a sphingosine-1-phosphate receptor modulator that suppresses lymphocytes exiting the lymph nodes, resulting in a reduced number of circulating lymphocytes, with the role of reducing neuroinflammation, and is administered starting from the age of 10 [99, 100]. It is used as the second line of treatment in RRMS that has not responded to the first line or as the first line of treatment in very active forms of the disease (characteristics of IFNb) and is available in the form of 0.25 and 0.5 mg tablets, 1 tablet/day, daily. The lower concentration is used for children weighing < 40 kg, while the 0.5 mg concentration is used for those weighing ≥ 40 kg. Frequent adverse reactions include: headache, increased GGT, nausea, vomiting, fatigue, infections, and lymphopenia [100]. Before administration, a cardiological, dermatological, and ophthalmological evaluation is conducted for possible adverse effects that may occur in these organs, and a complete vaccination schedule, including VZV, due to the immunosuppressive effect. The first dose is administered in the hospital because there is a risk of bradycardia, with monitoring of vital signs and ECG for six hours before and after those six hours [102]. Both in our study and in other studies, FTY had a good safety profile, good tolerability, and superior efficacy compared to IFNb, with few relapses and new lesions and a stable or improved EDSS [101].

The EDSS score for motor disability, SDMT for cognitive impairment, and PedQL for the quality of life of the patient and their family [108, 109] quantify the course of the disease.

There are favorable prognostic factors, such as: older age at onset (>12 years), onset with NO, female sex, EDSS 0 after the first relapse, annual relapse rate, number of new brain lesions, and low EDSS scores, RR form, long time between relapses, mild symptoms during relapses (sensory disturbances), absence of cognitive impairment and other associated diseases [10,

61], while unfavorable factors are the opposite of these, with the addition of obesity, vitamin D3 deficiency, and OCT changes. Efforts are made to improve the prognosis through early diagnosis and intervention, personalized treatment, a healthy and active lifestyle, avoiding harmful factors: smoking, alcohol, drugs, and maintaining an individual and family emotional balance [61].

Quality of life actually represents a complex of factors - it is the patient's perception of their health status in relation to the chronic condition they suffer from, and MS is a progressive disease with a negative impact on the quality of life of patients. The multidisciplinary team is the key to a better HRQoL for the patient and their family [47, 61, 110].

Studies conducted as part of the doctoral research

During the doctoral research, 4 studies were conducted:

The first study highlighted the particularities of clinical evolution, diagnostic difficulties, and treatment response in two patients with a rare and aggressive form of childhood multiple sclerosis - Baló concentric sclerosis [74].

The second study analyzed a group of six patients from the total cohort of 120 children who also have epilepsy, comparing their progression with that of the other 114 patients, with the aim of highlighting the heterogeneity of the etiology of epilepsy in children who associate these two entities, as it is not always secondary to multiple sclerosis; sometimes these conditions can merely coexist with varying degrees of mutual influence, with epilepsy actually having a genetic cause.

The third study identified the clinical characteristics of three groups based on the age of onset of MS: young age (<10 years), intermediate age (between 10 and 12 years), and adolescents (>12 years), with an emphasis on the particularities of the early-onset age group (<10 years) [35].

The fourth study, conducted on the entire studied cohort, evaluated the response to disease-modifying therapy (DMT), comparing patients who received injectable therapy with moderate efficacy (interferon beta) to those who received oral treatment with high efficacy (fingolimod), with a control group of 22 patients who did not receive specific treatment [102].

I mention that initially, the materials and methods used and general results regarding the demographic data of the cohort and the effect of external risk factors that can increase the risk of developing multiple sclerosis will be presented, followed by a detailed discussion of the results of the four studies listed above.

Material and method

The research was conducted at the "Prof. Dr. Alexandru Obregia" Clinical Psychiatric Hospital, within the Pediatric Neurology Department, during the period from January 1, 2018, to December 31, 2024, and included 120 patients with multiple sclerosis, under the age of 18, diagnosed

and/or monitored and treated in our clinic during this seven-year period.

The study was retrospective, observational, longitudinal, and was conducted in compliance with the current legislation, with the approval of the Ethics Committee of the "Prof. Dr. Alexandru Obregia" Clinical Hospital of Psychiatry (no. 8377/25.03.2025) and the obtaining of informed consent from the legal guardians of all patients included in the research. Before obtaining informed consent, the legal guardians were explained all the details of the study, the fact that clinical data from the files would be analyzed, as well as the method of disseminating the obtained results.

The inclusion criteria were: age < 18 years, a positive diagnosis of multiple sclerosis (meeting the McDonald 2017 criteria) - CIS or RRMS forms (the majority), having at least two admissions to our clinic, being monitored for at least 6 months, and not being included in other multiple sclerosis studies, with or without medication, during the research period.

The exclusion criteria were: uncertain diagnosis of multiple sclerosis or another form of multiple sclerosis (PPMS or SPMS), if they had only one continuous hospitalization, participation in clinical studies of multiple sclerosis, with or without medication, during this research.

The patients' medical records were studied, and demographic data as well as necessary medical data were extracted: presence of risk factors, form of MS, presence of BO, onset symptoms, number of relapses/year before and after treatment, number of new brain lesions/year before and after treatment, EDSS score/year before and after treatment, last EDSS value, type of treatment and number of treatments, cognitive impairment, presence of depression, etc.

At the onset of the disease, all patients underwent brain MRI on 1.5T machines, both native and with contrast agent, and screening of the entire spinal cord (cervico-thoraco-lumbar). Subsequently, the brain MRI was performed at 6 months, then annually or during relapses, at the initiation or change of treatment, while the spinal MRI was performed only at the cervical spine level annually or if the symptoms suggested a cervical lesion and before reaching the age of 18, this protocol being in accordance with the current international guidelines [91].

All patients underwent, in addition to the usual tests, blood tests to exclude infectious pathologies (Borrelia, EBV, HIV, HBV, HCV, TPHA, etc.) or autoimmune diseases (anti-AQP4 antibodies, MOG, anti-dsDNA, anti-TPO, etc.) which were negative. Additionally, all the children underwent a lumbar puncture with the determination of CSF biochemistry and oligoclonal bands (OCB). Depending on the associated pathology or the neurological symptoms during the episode, the subjects benefited from: endocrinological, ophthalmological, psychological, and psychiatric evaluations, as well as a physiotherapy program. Those with epilepsy underwent an EEG at the onset of the seizures, and then periodically as described in Study II.

Outcomes - basic demographic information and the influence of risk factors on the

examined cohort

The cohort includes 79 girls and 41 boys, with a girl-to-boy ratio of 2:1, and the age of onset ranged from 5 years and 2 months to 17 years and 6 months, with an average age of 14.29 years at disease onset and 14.99 years at diagnosis. Most of the patients come from urban areas (62.5%), with the geographical distribution being from Muntenia (28.3%), followed by Transylvania (23.3%), Moldavia (22.5%), Bucharest (14.1%), and Oltenia (8%).

Regarding risk factors, 17.5% were obese, with 71.4% (15 out of 21) being female. 14.1% reported the presence of a comorbidity in the month preceding the onset of the disease, with 23.5% of these testing positive for EBV (4 out of 17) and 17.6% for SARS-CoV-2, while the rest were not identified. Alcohol (0), drug (1.6%), and tobacco (5%) consumption were practically nonexistent, likely due to the presence of parents during the anamnesis. All evaluated patients had a vitamin D3 deficiency, with the majority, 63.3%, having a moderate deficiency, between 20-24 dl/ml.

64.1% of the subjects in the cohort have RRMS, while the rest have CIS. 80% of the participants have positive BO, and 36.4% of them are patients with CIS (35 out of 96), meaning that 81.3% of the children with CIS (35 out of 43) have positive BO and can be diagnosed with MS before the onset of a new relapse, as since 2017 their presence in CSF has been a diagnostic criteria.

Patients in the cohort had associated cognitive impairment in 24.1% and depression in 25.8%, only 5% had epilepsy, 3.3% Hashimoto's thyroiditis, and 1 patient had type I diabetes diagnosed prior to MS. Family histories, especially on the autoimmune side, were positive for the following pathologies: 8.3% (10) Hashimoto's thyroiditis, 7.5% (9) MS, 4% (5) type I diabetes, and 2 each with systemic lupus erythematosus, hypothyroidism, rheumatoid arthritis, psoriasis, and epilepsy. In 70% of cases, the affected relatives are first-degree, and in 30%, second-degree. In 3 cases, individuals from multiple consecutive generations are affected, and in 4 cases, an affected relative has two associated autoimmune pathologies.

The duration of disease monitoring during the study was between 1-3 years for 51.6% of the children, and 54.8% of them (34 out of 62) were monitored for 2-3 years, 26.6% were periodically evaluated for more than 3 years, 7.5% for more than 5 years, and 20% for 6 months to 1 year. ~20% of the patients (22) did not receive chronic treatment (the reason being the duration <1 year until the age of 18 with access to new molecules), while 39.1% (47) received treatment between 1-3 years, and 59.5% of these (28 out of 47) were treated for 1-2 years, the remaining 25.8% received specific medication for <1 year.

In **Study I** [75], I described the clinical characteristics, diagnostic difficulties, and treatment challenges in two cases of Balo's concentric sclerosis, with extensive cerebral lesions (> 2/3 cm), tumefactive, with massive perilesional edema and "tumor-like" behavior - mass effect, symptoms of

intracranial hypertension (ICH), or acutely installed motor deficits, a very rare form of MS, both in adults and children.

The first case was of a 15-year-old girl who presented to the clinic with episodic, intense headaches that had started 3 months earlier, initially with short episodes lasting 15 minutes, 3-4 times a week, spontaneously remitting, but with an increase in frequency and intensity in the last few weeks, with alarming signs: high intensity, duration ≥3-4 hours, not responding to anti-inflammatories, associated with photophobia/phonophobia and vomiting. Although the neurological examination was normal, due to the symptoms of increased intracranial pressure, a brain MRI was performed, which revealed an extensive tumefactive lesion in the right temporal lobe measuring 23 × 19 × 21.5 mm, suggestive of a demyelinating lesion, and another <1mm, with the appearance of an "active plaque." The spinal MRI was normal, and the spectroscopy, performed to differentiate a demyelinating disease from a glioma, showed inflammatory changes. Investigations continued on the autoimmune side, with the detection of positive BO in the CSF, while antiAQP4, antiMOG antibodies were negative and ATPO was elevated in the context of an associated autoimmune thyroiditis, leading to the diagnosis of Balo-type MS. He underwent pulse therapy with Methylprednisolone for 5 days, followed by Medrol for 2 weeks, with remission of symptoms. The clinical evolution was favorable in the following 2 and a half years, with rare episodes of headache, and the follow-up MRIs revealed new demyelinating brain and cervical lesions and a reduction in the large lesion. Due to the association with depression, she required psychiatric treatment and psychotherapy. After more than 2 years, she presented new symptoms with dysarthria and right facial asymmetry, and the neurological examination revealed right peripheral facial paresis and right hypoglossal nerve involvement. Corticosteroid pulse therapy was repeated with symptom remission, but when attempting to completely discontinue Medrol, limb paresthesias appeared, which is why corticosteroid therapy was continued. At the last evaluation, the EDSS was 2 - without cortisone (1 after one month from reinitiation), with normal intellect. IFNb was proposed as the first-line treatment, which had been suggested previously, but the patient and her family wanted to delay the treatment since she was soon turning 18 and had access to HET.

The second case is that of an 11-year-old girl who presented to the clinic with dysarthria and decreased muscle strength in the left hemicorp, which started on the day of presentation. The neurological examination in the emergency room revealed left hemiparesis with left central facial paresis, and the brain MRI showed a large tumefactive lesion in the right frontal lobe measuring 24x15.5x20.4 mm, as well as other small demyelinating lesions, raising suspicion of a demyelinating disease vs an infectious cause. The spinal MRI was within normal limits, the lumbar puncture revealed the presence of BO, and the blood tests showed negative antiAQP4 and antiMOG antibodies and positive IgG VEB. Pulse therapy with Methylprednisolone was performed, followed by Medrol

po for 2 weeks, with complete remission of the deficit. After 3 months, he presents with episodic paravertebral contractures, lasting minutes, a repeat brain MRI is performed, and an expansion of the brain lesion is observed, with massive perilesional edema. The neurosurgeon recommends spectroscopy, as in the first case, which shows an inflammatory aspect. The symptoms resolved spontaneously, and she was periodically monitored with imaging, showing a reduction in the size of the lesion. The next episode occurred at >3 years, also with left hemiparesis, resolved after corticosteroid therapy. IFNb was proposed, but the family wanted to delay chronic medication due to the injectable administration. After the third episode, 9 months later, the family opted for rituximab (RTX) treatment abroad, with favorable progress, no new relapses, and reduction of the lesion. And this adolescent also required psychiatric medication and psychotherapy for depression, her intellect was normal, and her EDSS remained at 0 between relapses and at the last evaluation.

In these cases, the differential diagnosis was primarily made with tumor formations, and the specific appearance of the lesion—concentric, tumefactive, and spectroscopy—was highly suggestive of demyelinating lesions [74, 75, 77] avoiding cerebral biopsy. The localization of the lesions was supratentorial, which was much more frequent than infratentorial. In both cases, the response to high-dose corticosteroid treatments was favorable, with complete remission of symptoms, a finding frequently reported in the literature, this treatment being considered "first-line" [71, 72, 111]. The clinical evolution was different; the first case followed a monophasic course, with only one relapse after >2 years, while the second case had a higher frequency of relapses similar to a typical MS case. Oligoclonal bands were positive in the CSF of both patients, and the MRIs of both cases showed typical lesions for MS, all of which are additional arguments for this condition [71, 72].

Regarding chronic treatment, for disease stabilization, the initiation of a DMT is recommended, although there is no guideline or protocol specifying which type of medication should be used, preferably a highly effective medication considering the potentially aggressive course of the form [72]. In the studied cases, the first patient wanted to delay IFNb until she was 18 years old, while the other received RTX abroad, with a favorable outcome (no relapses, no new brain lesions). RTX treatment is a well-chosen option because, in Balo's concentric sclerosis, oligodendrocytes and astrocytes are affected, leading to inflammation and demyelination [112], particularly involving peripheral B cells. RTX is a monoclonal anti-CD20 antibody that also acts on peripheral B cells, activating their anti-inflammatory role, with rapid reduction of demyelination and inflammation observed through control of relapses and absence of new brain lesions [105, 113].

In very rare pathologies, sharing experiences helps clinicians better manage similar cases, and the study's objectives were to characterize this rare form of MS and the desire for these examples to be useful to other colleagues, easing their diagnostic process and treatment choice.

The second study [95] aims to highlight the characteristics of the group with epilepsy and the heterogeneity of epilepsy etiology, which, in children with MS, is not always correlated with the autoimmune condition. There is also a genetic cause that can explain the occurrence of epilepsy in these children, in which case the two diseases are associated with varying degrees of mutual influence.

For this retrospective, observational study, 120 patients diagnosed with MS according to the McDonald 2017 criteria and treated at the Pediatric Neurology Clinic of Obregia Hospital during the period 2018-2024 were selected. Among them, 6 children (3 boys and 3 girls; mean age 9.8 years, range 4.6–15.3 years) had seizures or epilepsy. Data regarding the details of the seizures for the 6 children were collected: age at onset; time relative to the onset of MS; type, frequency, and duration of the seizures; whether the diagnosis of epilepsy was established (according to the ILAE classification), etc.; as well as data regarding MS for all the children in the study: age at onset and diagnosis of MS, duration of MS monitoring, annual relapse rate (ARR) before and after treatment, last EDSS. The patients underwent 1.5T native and K-enhanced brain MRIs, according to epilepsy and MS protocols, and those with epilepsy had electroencephalograms (EEGs) in the international 10-20 system with a double banana montage and an additional ECG channel; all 6 patients had ≥ 1 prolonged (3-4 hours) awake and sleep EEG, as well as multiple awake EEGs, the details of which were described. For statistical analysis, JASP 0.19 software was used, with tests including chi-square with Yates' continuity correction and Mann-Whitney U confirmed by the Shapiro-Wilk test. A p-value < 0.05 was considered statistically significant.

Characteristics of epilepsy: onset of seizures <10 years in 3 children, 1 at 10 years, and 2 in adolescence. In 4 children, the seizures began ≥2 years before MS, and in 2 of them near the onset of MS (2 weeks/9 months). In one adolescent, seizures appeared 2 weeks after the onset of MS, being controlled with levetiracetam (LEV). In a child under 10 years old, they started 9 months after the onset of MS, during the second exacerbation, in the form of a 4-hour left focal status epilepticus, and were treated with LEV for 6 months even though it was considered an acute seizure, not epilepsy. Both had their seizures controlled, and these were of autoimmune cause (secondary to MS). Among the subjects whose seizures preceded MS, two meet the criteria for a genetic form of epilepsy. The first adolescent was diagnosed with self-limited focal epilepsy with centro-temporal spikes (SeLECTS) at 6 years old, received treatment with valproic acid (VPA) for 3 years, with seizure control, and was two years without antiepileptic treatment (AE) at the onset of MS, while the brain MRI at 6 years old was normal. Another child presented with a generalized tonic-clonic seizure (GTCS) under conditions of sleep deprivation at the age of 13, and the EEG showed PVU-CVU type changes and photosensitivity at SLI between 10-30 Hz associated with myoclonus, leading to the diagnosis of idiopathic generalized epilepsy - juvenile myoclonic epilepsy (JME), controlled with LEV, with the onset of MS occurring 2 years after the epilepsy. The MRI performed

for epilepsy, and then dynamically, showed stationary demyelinating lesions until the onset of MS. The last two children in the group present a complex situation: they have epilepsy that started ≥ 6 years before MS, at the age of 4 years and 10 years, respectively, and have experienced multiple types of seizures (generalized, focal +/- secondary generalization), resistant to treatment, more frequent after the onset of MS, have generalized and focal changes on EEGs, and are on polytherapy with antiepileptic drugs, suggesting a genetic-autoimmune cause (genetic forms of epilepsy worsened after the onset of MS). All 6 had AED treatment, 4 had 1 AED that controlled the seizures, and 2 had polytherapy with persistent seizures.

Characteristics of MS: onset was with hemiparesis in 4 children, 1 with sensory disturbances, and 1 with ataxia, hemiparesis, and cranial nerve involvement. In 1 case, onset was before 10 years, in 2 cases between 10-12 years, and in 3 cases after 12 years. Two children have CIS, four have RRMS, and BO was positive in four children. All received DMT, 4 a single DMT (2 IFNb and 2 FTY), while 2 received multiple DMTs - initially IG, then IFNb, and finally FTY, with favorable progression. Those with RRMS had 2, 4, 7, and respectively 8 relapses, while those with multiple DMTs had 7/8 relapses. These 6 children were monitored for ≥2 years from the diagnosis of MS. To determine whether epilepsy is a risk factor for faster progression of MS and accumulation of disabilities, the annual relapse rate (ARR) and EDSS scores were compared between the group of patients with epilepsy and the group without epilepsy. It was found that, in the group with associated epilepsy, the last EDSS score showed a statistically significant increase in this group compared to the other ($p < 0.006$).

The results of this research demonstrate that pediatric patients with MS and epilepsy constitute a heterogeneous, complex group, making it difficult to define the precise relationship between these two entities. In children with MS, the inflammatory process is more active than in adults – and the early onset of MS implies a longer disease duration and the accumulation of disabilities over time [112].

On the other hand, epilepsy is one of the most common pediatric neurological pathologies ("the childhood disease") [114, 115], and genetic and structural causes are the most common etiologies of it. Zuo demonstrated the existence of a bidirectional causal relationship between MS and epilepsy [116].

Therefore, in this study, *2 patients have autoimmune seizures/epilepsy, 2 patients have genetic epilepsy, with MS as an additional factor, and 2 patients have a genetic-autoimmune etiology, mutually exacerbating each other. As a secondary objective, in this cohort, epilepsy is a risk factor for a higher EDSS score and the accumulation of disabilities, but the outcome was also influenced by the young age at MS onset, the long disease course, and the very active form of MS in*

these children. The presented study is a promoter for other multicenter research, aimed at validating the described hypotheses in the general population.

Study three [35] aims primarily to characterize the clinical features of pediatric patients with MS, dividing them into three groups based on the age of onset: early (<10 years), intermediate (10-12 years), and late (>12 years), with an emphasis on the peculiarities of the younger age group because, from the modes of onset to progression and response to treatment, these children present in a completely atypical manner. We deemed it necessary to introduce the intermediate age group, which combines elements from the other two groups, as it is a transitional period in the child's development that does not fully fit into either of the other two.

In this retrospective study, 120 children diagnosed and treated for MS, RR or CIS forms, participated at the Pediatric Neurology Clinic of Sp Obregia over a period of 7 years (2018-2024). The medical records of these patients were examined, and demographic data, age at onset, manifestations of the first attack, number of relapses, MRI appearance, EDSS score, and presence of BO were extracted. Cerebral and spinal cord MRIs at 1.5T were performed at onset and then according to the monitoring protocol.

The statistical analysis of the data was performed using SPSS version 22 and JAMOVI version 0.17.1.0. Descriptive statistics highlighted the clinical and demographic characteristics. Inferential analyses included chi-square tests to evaluate associations between categorical variables and the Kruskal-Wallis test to compare distributions across three age groups. To ensure consistency between groups, a random sample of ten patients with MS onset after the age of 12 was selected for subgroup analysis.

At the onset of MS - the first demyelinating episode, 11 patients were under 10 years old (group 1), 10 were between 10 and 12 years old (group 2), and 99 were over 12 years old (group 3), with a predominance of females in group 3 (2:1). In groups 1 and 2, the onset-to-diagnosis duration was up to 6-12 months due to the failure to meet McDonald criteria, compared to group 3 where the majority were diagnosed in <1 month, with statistically significant values, $p=0.005$, $p<0.01$. 80% of the subjects have RRMS, with most having a higher number of relapses before treatment, especially group 1 [31-33]. 27% of the patients in group 1 have a long duration between the first two relapses, even up to 3 years, but overall a higher number of relapses, differing from the reports of Kuppke and Kauth where the interval between the first two relapses is comparable between groups. In group 1, the onset was characterized by: ADEM-like episode 27.27%, ataxia 36.36%, and cranial nerve involvement 36.36%, while in group 3, the clinical manifestations at onset were: hemiparesis 14.14%, sensory disturbances 14.14%, optic neuritis 6.06%, and vestibular syndrome 23.23%, results comparable but not identical to the literature [31, 32, 50, 58]. Oligoclonal bands were positive in 63% of subjects with early onset and in 80-85% of those in groups 2 and 3 [6, 33 50].

85% of patients of all ages received DMT. 54% of group 1 received INFb and 18% FTY, and 1/3 switched to FTY or RTX. In group 2, 20% received RTX, 30% IFNb, and 50% FTY, while in group 3, 81% were treated with IFNb, 5% with FTY, results partially similar to Kauth's study [31]. EDSS begins to be modified after 2-3 years of illness, especially from the 4th year of MS in children with early onset ($p< 0.001$). With treatment, the EDSS score is slightly improved ($p>0.05$, $p=0.052$-0.584) or stationary in all three study groups ($p<0.001$), with statistically significant value. At the end of the study, in group 1, EDSS was 0 in 54% and slightly modified (1-2) in 36%; in group 2, 70% had EDSS 0 and 20% had EDSS 1-2; in group 3, 84% had EDSS 0 and 10% had EDSS 1-2, and 5 adolescents had EDSS 3, results similar to those published by Kauth [31]. In the early years of the disease, MRI showed many new lesions, especially in group 1, and after the introduction of DMT, a significant reduction in the size of the old lesions and the number of new ones was observed, consistent with the literature [6, 31-33, 58]. In group 1, 20% had borderline intellectual functioning, 20% had mild mental retardation; all had learning disabilities and executive function impairment [52, 61]. ≥50% of group 3 had psychiatric impairment - depression, anxiety [59, 117]. In group 2, we encounter a combination of clinical manifestations, imaging aspects, and treatment response present in the other two groups.

Ultimately, the characteristics of the early-onset group stand out: atypical symptoms especially at onset, motor and cognitive deficits accumulated over time, numerous and active brain lesions, all drawing the attention of experts to this special group - children with onset of MS <10 years. The study results highlighted a delay in the diagnosis of MS due to the atypical onset and progression, as well as changes in EDSS with the appearance of deficits after 3-4 years of progression in group 1.

The fourth study [102] aimed primarily to evaluate the response of patients in the studied cohort to disease-modifying treatment (DMT), demonstrating the superior efficacy and good safety profile of fingolimod (FTY) over interferon beta (IFNb). The subjects were divided into three groups: the IFNb group, the FTY group, and the no medication group (the control group). The response to treatment was quantified by measuring the number of relapses, new brain lesions, and the level of accumulated disability - the EDSS score, highlighted before and after the initiation of treatment.

The present study included 115 participants (5 excluded due to other treatments) aged <18 years, diagnosed with MS during hospitalization in the Pediatric Neurology Department of Obregia Hospital, 38 boys (33%) and 77 girls (67%), 9 with early onset (<10 years), 8 with onset between 10 and 12 years, and 98 with late onset (>12 years). 22 subjects were untreated, 79 were treated with IFNβ, and 14 with FTY. The 1.5T brain and spinal cord MRI was performed at onset and then according to the MS protocol. The statistical analysis of the data was performed using SPSS v 22.

The Kruskall Wallis and Chi-square association tests were applied to identify any differences between groups. From the group with IFNb, 15 children were randomly selected for group homogeneity, and the Chi-square test was applied.

20 untreated patients and 73 with IFNb had late-onset MS. In the group treated with FTY, 4 patients had early-onset MS, 5 had the onset of the disease between 10 and 12 years, and 5 had late-onset MS. 62 from the IFNb group initiated treatment within <6 months of diagnosis, while 11 from the FTY group started treatment within 6-12 months and 3 within 1-2 years due to the incomplete vaccination schedule required before starting FTY. The girl-to-boy ratio was 2:1 in the untreated and IFNb group and 1:1 in the FTY group. All treated patients received therapy for at least 1 year, most for 1-3 years.

The number of relapses was similar between groups before treatment and showed statistically significant differences over the 3 years of follow-up with treatment: 0 relapses in the FTY group, 58% without relapses in the IFNb group, results similar to those reported by Chitnis and Spelman [99, 118]. The duration between the first two relapses was similar between the groups. All patients had many new brain lesions prior to treatment, but with significant differences over the 3 years of treatment: a reduction of >50% in the IFNb group and 67-80% in the FTY group, percentages similar to Arnold's report [119]. No significant differences in EDSS scores between groups before treatment, but after its initiation, 14% of patients with IFNb had mild impairment and 4% moderate after 1 year, later 10% had mild disability and 2% moderate. For the FTY group, 20% showed mild deficits and 7% moderate deficits after 1 year, then 7% showed mild deficits.
The results indicate a 30% improvement in the IFNp group and a 70% improvement in the FTY group after 1 year, which is maintained, confirmed by Piri Cinar and other authors [120-122]. Also highlighted low EDSS values in children and adolescents treated with fingolimod. Adverse reactions were mild, with a pseudo-flu-like appearance for IFNb and lymphopenia for FTY, confirming a good safety profile [105, 123].

Early initiation of disease-modifying therapy (DMT) is essential in pediatric-onset multiple sclerosis (POMS) to improve long-term outcomes. This study has demonstrated the superiority and good safety profile of FTY in the treatment of pediatric MS compared to IFNb and supports the need for using HET in the treatment of MS in children.

Conclusions

The main objective of this study was *to characterize clinically, radiologically, and in terms of response to available specific treatments, pediatric multiple sclerosis in Romania.*

Therefore, we highlighted the clinical features based on the age of onset of MS, with an emphasis on describing the group with early onset (<10 years) due to atypical progression; we described rare forms of MS, with tumefactive lesions, which pose diagnostic and treatment

challenges - Balo's concentric sclerosis; we explored the complexity of the etiology of epilepsy in children who associate the two entities: MS and epilepsy, and, last but not least, we underscored the necessity of initiating DMT as quickly as possible, especially HET, demonstrating the superior efficacy and good safety profile of FTY in the treatment of pediatric MS compared to IFNb for a favorable progression, with the best possible disease control and a good long-term quality of life for patients and their families.

I point out that such a study, on a group of children with MS, has not been conducted so far in our country.

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