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Multiple sclerosis' evolution of paediatric patients in adult life: A preliminary study

Danai-Niki Giourgali[1,2,*]

[1] University of Medicine and Pharmacy 'Carol Davila', Medical School, Bucharest, Romania
[2] Emergency University Hospital of Bucharest (SUUB), Romania

***Corresponding author**
Danai-Niki Giourgali, MD, Zehntstraße 10, Mannheim, Germany, Postal code 68169. Tel: + 4917662351799
E-mail: danaegiourgaly@gmail.com

Abstract

Background - Nowadays, multiple sclerosis is considered to be the most common immune-mediated, inflammatory, demyelinating disease of the central nervous system. Approximately 2.1 million people suffer from this disease worldwide.
Scope - The presented article is a retrospective observational preliminary clinical study, being based upon fourteen patients.
Materials and methods – These patients were initially evaluated and diagnosed in the 'Neuropaediatric department' and then admitted to the 'Emergency University Hospital of Bucharest' (SUUB), after the age of 18 years. The aim of this clinical study was to retrospectively assess the evolution of multiple sclerosis from the moment of its initial clinical manifestation on these paediatric patients into adult life.
Results - For each of these patients, a study sheet was designed, according to which every patient was evaluated based upon a variety of parameters.
Conclusions – The majority of the data obtained from this preliminary clinical study is congruent with the literature. Nevertheless, the presented article emphasizes the possibility of a Cytomegalovirus (CMV) - viral infection to be a causative agent of multiple sclerosis and not a protective factor instead. Even though epileptic seizures are considered to be an unusual manifestation of multiple sclerosis, a specific case of one paediatric patient with multiple sclerosis is being presented, who also suffered from general tonic-clonic seizures.

KEYWORDS
multiple sclerosis, early-onset, glucocorticoids, disease- modifying therapies, adverse reactions, retrospective observational clinical study, preliminary study, statistical analysis

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1. INTRODUCTION

In a typical case of MS, young adults are mostly affected [1]. However, paediatric MS, also named Early- Onset MS (EOMS) or Juvenile MS, has an increasing prevalence, accounting for about 5% of the cases in total and affecting patients being younger than 18 years of age [2]. It has been indicated that female children and adolescents, being older than 12 years old and younger than 18 years of age, are getting affected by EOMS more frequently

than their male peers in a ratio approximately 2.8 [2,3]. In patients younger than 6 years of age, the female-to-male ratio with multiple sclerosis is proven to be approximately 0.8/1 [4].

Various parameters play an important role regarding the incidence and prevalence of multiple sclerosis, such as: the race of the patients, the region where they live in analogy with its latitude, the coexistence of various other autoimmune diseases and the presence of genetic susceptibility and different viral infections [5,6,7]. The aforementioned viral infections are indicated to be caused by various viruses, for instance the Epstein- Barr virus (EBV), the Rubella virus and the Varicella Zoster virus (VZV) [5,6,7]. There are some other case- control studies indicating that some vaccinations can be associated with an increased risk of developing MS [5]. Various hypotheses have been made, emphasizing that a cytomegalovirus (CMV)- viral infection, the ultraviolet radiation and the 25-hydroxyl-vitamin D of the sunlight can even act as protective factors against multiple sclerosis [5,8,9,10].

The neuropathological hallmark of multiple sclerosis is the synchronous existence of not only focal demyelinating plaques and inflammation, but also of gliosis having occurred throughout the entire central nervous system (CNS), along with simultaneous partially- preserved neuronal axons [11,12]. Inflammation, demyelination and axonal degeneration are the major mechanisms of multiple sclerosis [13]. It is considered that this disease begins as an inflammatory, immune-mediated disorder, characterised by autoreactive lymphocytes, followed by microglial activation and chronic degeneration [14]. In reference to the pathophysiology of MS in paediatric patients, it has been investigated that they present the same two types of antibodies as the adult patients: the anti-myelin oligodendrocyte glycoprotein antibodies (anti-MOG Ab) and the anti-myelin basic protein antibodies (anti-MBP Ab) [4,15].

Moreover, multiple sclerosis can be subdivided into two distinct phenotypes, namely the relapsing-remitting and the progressive diseases [16]. There are four clinical subtypes in total: the Clinically-isolated syndrome (CIS), the Relapsing-remitting MS (RRMS), the Secondary-progressive MS (SPMS) and the Primary-progressive MS (PPMS) [16,17]. The clinical manifestations of multiple sclerosis in paediatric patients are similar with those in the respective adult patients [2,18]. More particularly, they can vary from optic neuritis, diplopia and partial transverse myelitis to brainstem and cerebellar dysfunction syndromes [2,18]. However, it has been investigated that the Clinically- isolated syndrome (CIS) affects the paediatric patients more frequently than the adult ones [18].

The diagnosis of multiple sclerosis is based on the clinical history and the neurological examination of the patient, as well as supportive MRI findings and ancillary laboratory findings - cerebrospinal fluid (CSF) testing [1,19,20]. More precisely, the positive diagnosis of multiple sclerosis ultimately relies on the McDonald Criteria, being determined by the neurologist W. Ian McDonald [21,22]. The Magnetic Resonance Imaging (MRI) is considered to be the 'gold standard imaging technique' for the identification of demyelinating lesions [23,24].

It is important to perform MRI of the brain, with and without gadolinium contrast, and MRI of the entire spinal cord [1,24]. The physician should check for typical periventricular lesions, especially being observed in FLAIR sequences- for instance, the 'Dawson's fingers' and the commonly known as 'black holes' which prove the existence of a permanent neuronal axonal loss and have a low signal on T1-weighted images [25]. The differential diagnosis of MS with other autoimmune inflammatory demyelinating diseases of the central nervous system (CNS), such as the neuromyelitis optica spectrum disorders (NMOSD) and the progressive multifocal encephalopathy (PME), should always be thoroughly examined [25,26].

Regarding the treatment of an acute MS attack, a high-dose of glucocorticoids, mainly of methylprednisolone (Solumedrol), is considered to be the main course of treatment for an acute MS attack [27]. If there is an intolerance to the aforementioned method, poor venous accessibility or even a preference to self-injection, then the utilisation of purified bovine or porcine adrenocorticotropic hormone (ACTH) is further suggested as an alternative option [28].

Considering the prolonged treatment of multiple sclerosis, initiation of a disease-modifying therapy (DMT) is recommended to decrease the number and the duration of MS relapses, ultimately reducing the accumulation of disability from the disease [29]. In paediatric patients who have developed RRMS, the initial treatment-of-choice is DMTs [30]. Nevertheless, this decision is taken after careful consideration of the related benefits and risk factors of the respective treatment from the patient themselves and their family [30].

As initial therapy with DMTs, the most preferable options are the medications with high or intermediate efficacy, which lead to the decrease of MS exacerbations and the reduction in the appearance of new active brain lesions [31]. For instance, such medications can be Rituximab, Fingolimod (Gilenya) and Dimethyl fumarate [31]. Interferons- beta drugs (Avonex, Rebif, Betaferon) and Glatiramer acetate (Copaxone) are considered to have lower efficacy

[30,31]. However, the aforementioned preferred drugs have more serious adverse reactions [30,31].

As an alternative option, it is suggested the initiation of an older injectable DMT with lower efficacy for patients with mild-to-moderate RRMS and minimal associated functional deterioration [29, 30,31]. It is also suggested the subsequent transition into an oral or intravenous DMT with intermediate or high efficacy respectively for patients, who experience new MS flairs or present new active lesions on brain MRI [29, 30, 31]. Older injectable DMTs are represented by Glatiramer acetate (Copaxone), Interferon beta-1a (Avonex, Rebif), Interferon beta-1b (Betaferon) and Peginterferon beta-1a [31].

Furthermore, monitoring of the patients' response to DMT treatment is very important, both clinically and with the help of neuroimaging parameters at baseline and after one, three and six months following the specific treatment's initiation, as well as every six months after this point [30]. In paediatric cases without MS exacerbations, with an associated stable clinical status, a clinical and a neuroimaging evaluation every year is considered to be sufficient [30, 32]. However, independently of the patient's clinical status, if active lesions appear on a brain MRI, then the alternation of the DMT treatment into another, more aggressive immunomodulatory drug with higher efficacy is compulsory [30, 33]. In this case, the MRI paraclinical evaluation of the respective patient should be repeated every six months to a year, following the initiation of the new treatment with DMT [30,33].

A treatment failure is determined by at least two MS relapses within one year, based upon clinical or MRI evidence, or at least two new active T2 or contrast-enhanced lesions on brain MRI [30]. In such a case, it is suggested the alternation of the treatment from a lower efficacy DMT, such as Glatiramer acetate (Copaxone) or Interferons-beta (Avonex, Rebif, Betaferon), to another DMT with intermediate or higher efficacy, for instance Fingolimod (Gilenya) or Rituximab [30]. In a similar manner, in case of a poor response of a patient with MS to an oral DMT agent, then the alternation of the treatment to a high-efficacy infusion DMT, such as Rituximab or Natalizumab (Tysabri), is proposed [30]. More precisely, if a patient does not respond properly and has a bad evolution under treatment with a recombinant human Interferon beta-1a (Avonex), then their treatment should be switched into a higher-dose DMT, such as a recombinant human Interferon beta-1b (Betaferon), a recombinant human Interferon beta-1a (Rebif) or Glatiramer acetate (Copaxone) [30].

Pregnancy and a late postpartum period can play a protective role against multiple sclerosis [34]. In addition, it has also been indicated that paediatric patients with an Early-onset MS (EOMS) have a higher risk of developing numerous acute relapses of multiple sclerosis than the adult patients with MS [30, 35]. However, paediatric patients are more likely to have a slower progression of the disease, even though they will ultimately suffer from neurological and physical deterioration at an earlier age, compared to the patients who underwent an adult-onset multiple sclerosis [36].

In reference to the paediatric patients with multiple sclerosis, an increased relapse rate within the first two years from the initiation of this demyelinating disorder and a progressive course at the level of its onset can contribute as negative prognostic factors [35, 36]. On the contrary, paediatric patients with an Early-onset multiple sclerosis (EOMS) can have a more promising and better prognosis, when they are being treated by various disease-modifying therapies (DMTs) [36].

The evolution of EOMS in the adult life is the main purpose of the presented article, with the aim to determine any differences in a variety of parameters regarding the paediatric-onset and the adult-onset multiple sclerosis. As such parameters are mentioned their epidemiology, their pathogenesis and environmental triggers, the predominance of each clinical phenotype of this disease in reference to the gender and age of the patients, the course of each clinical form of multiple sclerosis and the manifestation of fatigue, depression and cognitive impairment.

The presented article additionally aims to identify any differences regarding the outcome of the various paraclinical investigations in paediatric and adult patients with multiple sclerosis, concerning for instance their Magnetic Resonance Imaging (MRI) findings, their cerebrospinal fluid (CSF) profile and their Evoked Potentials' (EPs) results. Moreover, the main course of treatment is going to be described for each form of multiple sclerosis, in reference to an acute exacerbation or a chronic disease. Furthermore, this article focuses not only on the evolution and the prognosis of each patient, but also in thoroughly describing the characteristics of multiple sclerosis during pregnancy.

2. MATERIALS AND METHODS

This retrospective observational clinical study is based upon 14 different patients with multiple sclerosis, with the aim of retrospectively assessing the evolution of this demyelinating, inflammatory disease during their lifetime, more precisely from the moment of their first clinical manifestation as paediatric patients to adulthood. These 14 patients

were initially evaluated and diagnosed in the 'Neuropaediatric department' and then they were admitted to the 'Emergency University Hospital of Bucharest' (SUUB), after the age of 18 years old.

For each of these patients, a study sheet was designed (Table 1), according to which every patient was individually evaluated based upon a variety of parameters. More particularly, these factors were: their gender, their current age, the type of their first clinical symptom and their specific age upon its appearance, their age during their initial diagnosis, the results of each paraclinical investigation that took place in the concept of their differential diagnosis, the appearance and the evaluation of any existent secondary clinical manifestations, the clinical signs and symptoms of the paediatric patients who initially presented with a clinically-isolated syndrome and the assessment of its evolution into a different clinical phenotype of multiple sclerosis, the treatment plan for each individual patient, the assessment of the evolution of their disease into adulthood, their individual prognostic features and their specific clinical status being provided through their anamnesis.

Table 1: Study sheet of the retrospective clinical study. Source: Author's elaboration.

Name of the patient:	
Gender:	
Age:	
Age of the first symptom:	
Age of the initial diagnosis:	
Type of the first symptom:	
Number of attacks:	
Clinical manifestations of each attack:	
CSF profile:	
Optical Coherence Tomography (OCT) findings:	
Motor Evoked Potentials (MEPs) findings:	
Autoantibody testing:	
Cerebral MRI findings:	
Medullary MRI findings:	
Expanded Disability Status Scale (EDSS):	
CIS evolution into MS:	
Type of treatment:	
Evolution of MS into adulthood:	
Prognosis:	
Anamnesis:	

According to the results of this aforementioned retrospective clinical study based upon these 14 different patients, a statistical analysis was carried on. Afterwards, specific conclusions were made, considering the manner of evolution of multiple sclerosis from these paediatric patients into adulthood and the prognostic features of this particular disease in relation to its specific treatment course.

3. RESULTS OF THE STATISTICAL ANALYSIS

Among these 14 patients, there was no predominance being noticed regarding their gender. There have been equally encountered seven female and seven male patients, who were characterised by various clinical manifestations of this demyelinating, inflammatory disease. According to recent research data among various patients with multiple sclerosis, it has been estimated a predominance of the female gender [2]. Nevertheless, due to the limited number of patients having participated in the clinical study, no difference in the female-to-male ratio of patients with multiple sclerosis can be assessed between the data of this preliminary study and the literature.

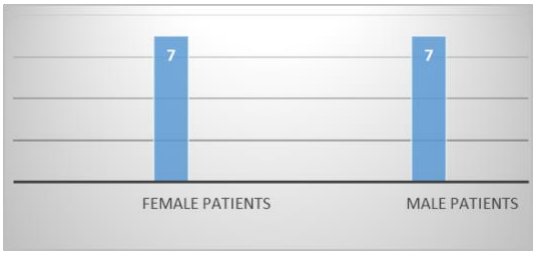

Figure 1: Equal Gender Predominance in EOMS. Source: Author's elaboration.

Several studies have indicated that less than 1% of the total cases of MS are diagnosed in patients who are younger than 10 years old, constituting about 20% of the total amount of paediatric cases [2, 4]. According to this retrospective clinical study, only one out of the 14 patients had their initial diagnosis of multiple sclerosis before the age of 10 years, more specifically when they were 8 years old, constituting merely the 7.14% of this particular group of patients with Early-Onset Multiple Sclerosis (EOMS). The same percentage appeals to the number of patients who were officially diagnosed with EOMS for the very first time at the age of 10 years, 13 years, 14 years and 17 years and 10 months, respectively. Moreover, only two out of these 14 patients with multiple sclerosis

experienced their first official diagnosis at the age of 15 years and 16 years respectively, indicating that only 14.29% of this aforementioned group had their first attack during that specific age.

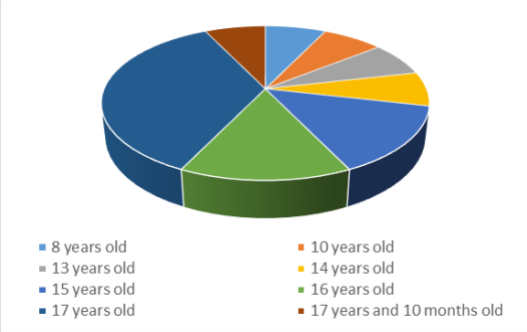

Figure 2: Age of initial diagnosis with EOMS.
Source: Author's elaboration.

In addition, five out of these 14 patients had their diagnosis of multiple sclerosis when they were 17 years old, constituting the 35.72% of this precise group of patients participating in the aforementioned clinical study.

According to the respective retrospective clinical study, only one patient experienced their initial clinical manifestation before the age of 10 years, more precisely when they were 8 years old, thus constituting the 7.14% of this group of patients with EOMS. The same percentage appeals to those patients who presented their very first neurological episode at the age of 10 years, 12 years, 15 years and 17 years and 10 months, respectively. Only two out of these 14 patients had their initial clinical manifestation of multiple sclerosis at the age of 13 years, 14 years and 17 years, contributing to the 14.29% of the same group. Nevertheless, only three out of these 14 patients experienced their primary attack of multiple sclerosis when they were 16 years old, indicating that 21.43% of them encountered their initial clinical manifestation of EOMS at that particular age.

Additionally, it was observed during this clinical study that not all 14 patients presented the same form of multiple sclerosis as their initial manifestation. More specifically, three out of these fourteen patients experienced primarily a Clinically-isolated syndrome (CIS), before its progression into Relapsing-Remitting Multiple Sclerosis (RRMS), constituting the 21.43% of the respective group of patients. Two out of these three patients with CIS presented a left hemibody ataxic syndrome as their initial manifestation of multiple sclerosis, which indicates a motor deficit of their left limbs, constituting 66.67% of this specific group. Only the remained one patient with CIS, therefore the other 33.33% of this small group, experienced initially left hemiparesis.

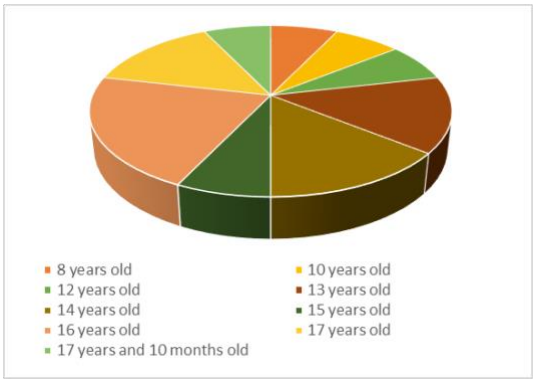

Figure 3: Age of initial clinical manifestation of EOMS.
Source: Author's elaboration.

Moreover, merely one patient, meaning 7.14% of the entire group, manifested initially RRMS, which ultimately progressed into Secondary-Progressive Multiple Sclerosis (SPMS). The majority of these fourteen patients, more specifically ten out of them, manifested RRMS as their initial type of multiple sclerosis, which did not progress later on into another form of MS, constituting the 71.43% of the given patients.

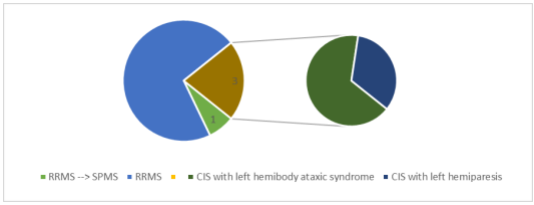

Figure 4: Clinical phenotype of Multiple Sclerosis as initial presentation.
Source: Author's elaboration.

Furthermore, all these fourteen patients presented motor deficits either as their initial clinical manifestation of multiple sclerosis or during the course of their disease. During the same interval of the manifestation of this demyelinating disease, three of them presented severe spasticity and thirteen patients experienced subjective sensitive sensation paraesthesia (described as burning and prickling sensation). Six patients in total experienced ataxia and equilibrium disturbances, among whom three of them presented cerebellar ataxia with coordination disturbances and the rest three of these patients manifested vestibular ataxia with a vertiginous syndrome.

Twelve of these patients experienced various brainstem symptoms (muscle weakness, difficulty speaking, nausea and headache) and six of them suffered from transverse myelitis. Nine patients from this clinical study manifested optic neuritis either initially or during the development of their inflammatory, immune-mediated disease, while only one patient manifested optic nerve atrophy. Eight of these patients had a decrease in their visual acuity, five patients experienced diplopia and seven of them were clinically observed to have nystagmus.

Two patients had concentration difficulties as cognitive impairment, while other two of them had language disorders. Only one patient presented epilepsy as an unusual manifestation of multiple sclerosis [16]. Six out of these fourteen patients suffered with micturition disturbances, six patients complained of fatigue or hypoaccusis, one patient experienced migraine and other two of them had headache. The clinical manifestations of these previously-described fourteen patients with multiple sclerosis during the course of their disease can be evaluated in Figure 5.

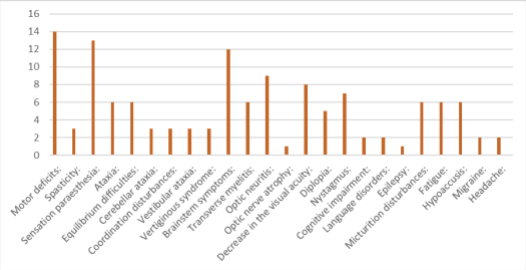

Figure 5: Clinical manifestations during the course of Multiple Sclerosis.
Source: Author's elaboration.

More specifically, three patients of this group initially presented with a Clinically-isolated syndrome (CIS). Two out of these three patients had experienced motor deficits as their first clinical manifestation of CIS, while the third patient had depicted multifocal symptoms as their initial clinical presentation. More precisely, this patient had presented a motor deficit in association with equilibrium disturbances and paraesthesia.

Along the course of their disease and the evolution of their Clinically-isolated syndrome (CIS) into Relapsing-Remitting Multiple Sclerosis (RRMS), all of these three patients presented a deterioration of their motor function and coordination disturbances. Two of them manifested paraesthesia, equilibrium disturbances, ataxia and diplopia. Only one of these patients suffered from spasticity, optic neuritis, nystagmus, language disorders and micturition difficulties. The initial clinical manifestation of each patient, who experienced a Clinically-isolated syndrome, and the presentation of their further clinical signs and symptoms along the evolution of CIS into RRMS can be observed in Figures 6 and 7.

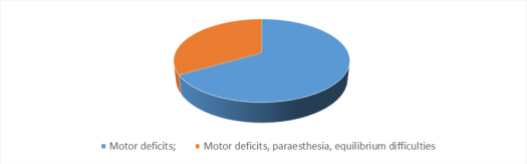

Figure 6: Initial clinical manifestation of a Clinically-isolated syndrome.
Source: Author's elaboration.

Among the three patients of the clinical study who manifested a Clinically-isolated syndrome (CIS), the first patient with CIS presented his second MS attack one year later, thus progressing into a Relapsing-Remitting Multiple Sclerosis (RRMS). However, he started receiving a disease- modifying therapy (DMT) with an interferon beta-1a (Avonex) only four months after his first MS flair and diagnosis with CIS.

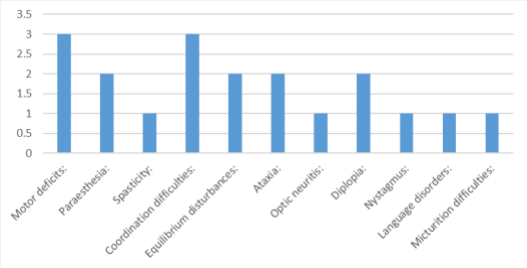

Figure 7: Clinical manifestations during the evolution of CIS into RRMS.
Source: Author's elaboration.

Moreover, the second respective patient presented his first attack as CIS in July 2011 and progressed into RRMS with his second MS neurological episodes after one year and five months, in December 2012. However, he began receiving treatment with an interferon beta-1a (Avonex) in September 2011, meaning only two months after his first manifestation of a Clinically-isolated syndrome (CIS). On the contrary, the third and last patient of the aforementioned study presented her first neurological episode of a clinically-isolated syndrome in January 2018, but she did not receive any treatment with a disease-modifying therapy (DMT) until one year later, when she began treatment with an interferon beta-1b (Betaferon). She also experienced her second flair of multiple sclerosis eight months after her first episode, in August 2018, thus

developing a Relapsing-Remitting Multiple Sclerosis (RRMS).

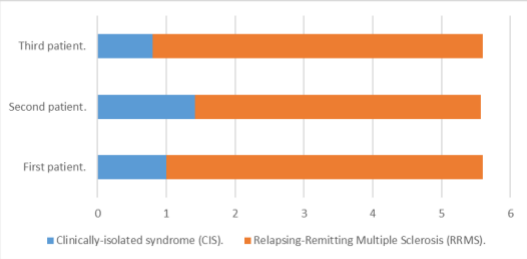

Figure 8: Age of debut of Relapsing-Remitting Multiple Sclerosis (RRMS), progressing from a Clinically- isolated syndrome (CIS).
Source: Author's elaboration.

All these characteristics of the three aforementioned paediatric patients of the clinical study, who manifested a Clinically-isolated syndrome (CIS), can be thoroughly observed in Figures 8 and 9. In Figure 8, the beginning of the x-axis depicts the onset of the Clinically-isolated syndrome (CIS) for each of these three paediatric patients, respectively.

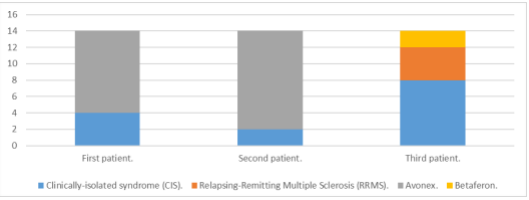

Figure 9: Age of debut of a disease-modifying therapy (DMT), after the manifestation of a Clinically- isolated syndrome (CIS).
Source: Author's elaboration.

Another important characteristic of the evolution of this demyelinating, inflammatory disease, which was retrospectively estimated and thoroughly analysed during this clinical study, was the number of neurological episodes that each patient had experienced in total during the course of their disease. It is already known that the more the neurological episodes that a patient with multiple sclerosis has gone through, the worse their evolution and their prognosis may be [16].

According to the aforementioned study, three patients had presented two neurological episodes in total during the evolution of their disease, other two patients had experienced three attacks until the moment of their last examination, two different patients had gone through four flairs and other two of them had already seven neurological clinical episodes in total. Only one patient had eight attacks till the moment of their most recent clinical assessment, whereas two other patients had experienced ten separated clinical episodes and another patient had even more than ten clinical attacks until the moment of their last clinical evaluation. However, only one patient had more than sixteen neurological episodes, which directly underlines the fact that the respective patient had a very bad evolution of their disease till their last evaluation.

On the one hand, half of the paediatric patients, meaning seven out of these fourteen previously-mentioned patients, presented zero new neurological episodes of multiple sclerosis within the first two years of this demyelinating disease. On the other hand, only one patient presented one new MS attack in the first two years after their initial clinical presentation of multiple sclerosis, even if that patient was under treatment with an interferon beta-1a (Rebif), while three other paediatric patients manifested two new MS flairs within the same interval. One other patient experienced four to five new neurological episodes, another one manifested exactly five MS attacks and one last patient even presented five to seven new flairs of multiple sclerosis.

It was also observed that the more the neurological episodes of multiple sclerosis that a patient was experiencing, the worse their neurological and physical deterioration was becoming, therefore leading to a worse evolution and a bad prognosis of their inflammatory, demyelinating disease. All these important observations are depicted in Figures 10 and 11.

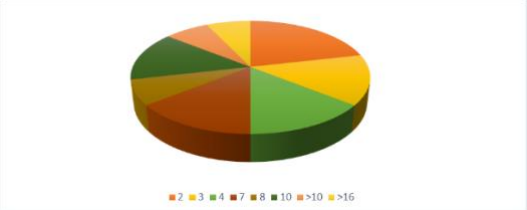

Figure 10: Total number of neurological episodes.
Source: Author's elaboration.

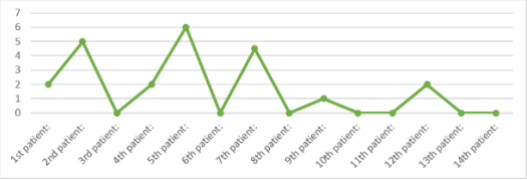

Figure 11: Number of MS attacks within the first two years.
Source: Author's elaboration.

In reference to the bibliography concerning the disability measures, the Kurtzke Disability Status

Scale (DSS) and the Expanded Disability Status Scale (EDSS) are frequently used, in order to estimate the severity of the signs and symptoms of the patients with MS [16]. These indices use numbers from 0 to 10, ranging from a normal examination and functional capacity of the patient to their death due to multiple sclerosis [16]. It is noted that the progressive disability of the patients is not linear, with a particular decrease in their basic functional status when the patient has achieved a score above the fourth scale [16].

More precisely, when the EDSS score is equal to or above the fourth scale, then the outcome is almost entirely dependent on the walking capacity of the patient [16]. These indices do not particularly measure the degree of potential cognitive impairment, visual loss and hand weakness [16]. It has been proven that each increase in the EDSS score has a different impact on the quality of life (QoL) of every patient [16]. According to the results of the clinical study, the following EDSS score can be observed for each patient (Fig. 12).

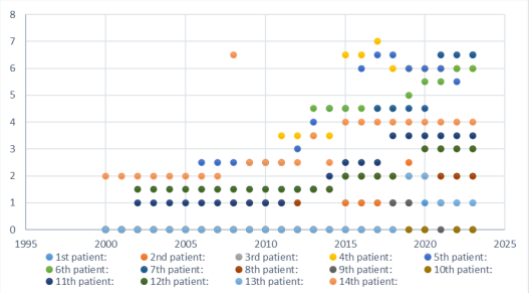

Figure 12: Expanded Disability Status Scale (EDSS).
Source: Author's elaboration.

Considering the relation between the EDSS score and the prognosis of each patient, Figure 13 may be carefully observed. More precisely, the prognosis is estimated on the y-axis, where it is indicated that the prognosis of each patient is characterised as more favourable as the numbers are getting increased on the y-axis. For instance, the best possible prognosis for a patient with multiple sclerosis is estimated when the y-axis is identified with the number 8. On the x-axis, the EDSS score is outlined. It can be easily evaluated that when the EDSS score of a patient with multiple sclerosis becomes bigger, then their prognosis gets worse instead. Therefore, it is underlined that the EDSS score has a reverse relation with the prognosis of each patient.

As it was thoroughly investigated during this retrospective clinical study, some paediatric patients with multiple sclerosis presented with general epileptic seizures or even a cerebellar and a vestibular syndrome, during the course of their disease. These particular patients were associated with a more significant deterioration of their medical clinical condition and new neurological episodes, in comparison with the other patients. Epilepsy is considered to be an uncommon, unusual presentation of multiple sclerosis [16].

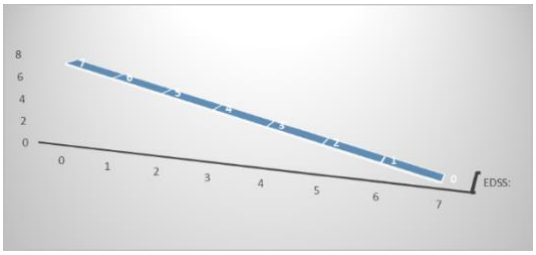

Figure 13: EDSS- Prognosis relation.
Source: Author's elaboration.

Therefore, it has been concluded that the presence of either epileptic seizures or cerebellar and vestibular syndromes at any time during the course of their disease is reversely associated with the evolution and the prognosis of the respective patient with multiple sclerosis. The more increased the number of epileptic seizures, of a cerebellar or a vestibular syndrome that a patient has been experiencing is, the worse their evolution and consequently their prognosis are.

Concerning the impact of coexistent or past infections in the actual manifestation of multiple sclerosis among the aforementioned fourteen patients, only four of them had not presented any type of acute or previously- encountered viral infection at the point of their paraclinical investigation. According to the results of the serum antibody testing of the remained ten patients, it was established that four of them had experienced in the past an infection caused by the Varicella zoster virus (VZV), two of them had a past infection with Herpes Simplex virus 1⁄2 (HSV½), other two of them were diagnosed with a previous infection by the Rubeola virus and only one of them was observed to have an acute infection with mumps, caused by the urlian virus.

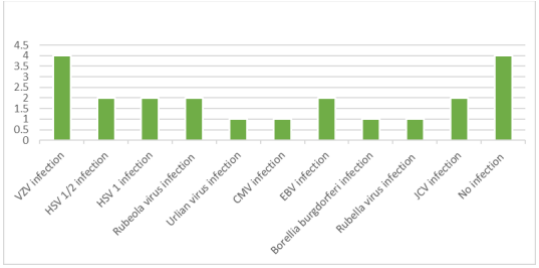

Figure 14: Type of infection as a risk factor for EOMS.
Source: Author's elaboration.

Additionally, two out of these fourteen patients had suffered before from an infection by the Herpes simplex 1 virus (HSV1), two of them had a previous manifestation of an infection by the Cytomegalovirus (CMV) and one of them was currently suffering from Lyme disease, being caused by the spirochete Borrelia burgdorferi. One patient had previously an infection caused by the Epstein-Barr virus (EBV) and another patient with multiple sclerosis was also diagnosed with a past infection by the Rubella virus. Two more patients in this group were diagnosed with anti-JCV Ab, proving that these patients were previously or currently infected by the JC virus (JCV), which is a predictive factor of Progressive Multifocal Leukoencephalopathy (PML) for multiple sclerosis' patients having been treated with natalizumab (Tysabri) [29].

Furthermore, it has been noticed that even without the surveillance of a specific treatment, most of the relapsing episodes in multiple sclerosis are characterised by a following spontaneous recovery period, which can be of a variable degree [14]. The primary goal of each treatment plan is to shorten the recovery period from the MS exacerbation and to decrease its disabling effect on the patient [14]. However, the variable types of acute treatment of multiple sclerosis' attacks do not significantly benefit the patient long- term, regarding the risk of occurrence of yet another flair and the degree of their neurological disabling impact [14].

Therefore, the education of each patient with multiple sclerosis about the main clinical manifestations of MS relapses, the various treatment possibilities and the expected results is considered to be a very important factor, regarding the acute management of MS relapses [14]. Another important factor, which should be taken into account in order to avoid unnecessary treatment, is the presence of pseudorelapses, which should always be distinguished from the real acute MS relapses [14].

According to the clinical study, the number of patients that had received each specific type of drug during their entire course of treatment was estimated. In reference to their treatment for an acute MS attack, 13 of these paediatric patients were treated with methylprednisolone (Solumedrol), two patients received dexamethasone and other two patients in total underwent therapy with Prednisone.

Concerning their prolonged treatment of multiple sclerosis with a disease-modifying therapy, five patients in total underwent therapy with an interferon beta-1a (Avonex) during their evaluation. Four out of these fourteen patients took an interferon beta-1b (Betaferon/Extavia) at one point during the manifestation of their disease and five patients had undergone treatment with teriflunomide (Aubagio). Two of them had taken fingolimod (Gilenya), whereas five patients had received an interferon beta-1a (Rebif) at one point during their course of treatment due to multiple sclerosis. Another patient was administered with dimethyl fumarate (Tecfidera), one different patient had taken Plegridy and another one had received natalizumab (Tysabri).

Moreover, it has been estimated that four of these patients underwent treatment with glatiramer acetate (Copaxone), one patient with Ponesimod, another one with Siponimod and three patients in total had been treated with ocrelizumab (Ocrevus). In addition, one patient experienced epileptic seizures during the course of their disease, thus being treated with gabapentin (Gabaran). All the aforementioned observations, regarding the treatment of these patients for an acute MS attack and their prolonged treatment of multiple sclerosis with the help of various disease-modifying therapies (DMTs), can be estimated in Figures 15 and 16.

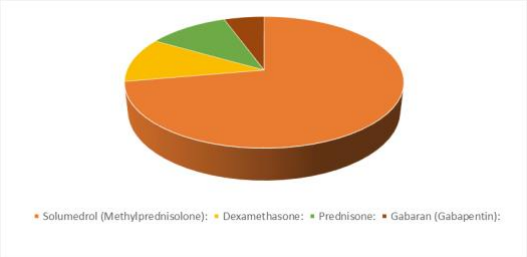

Figure 15: Treatment of an acute MS attack.
Source: Author's elaboration.

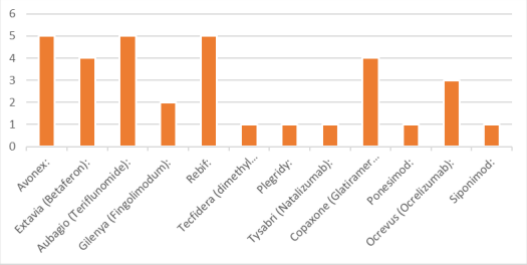

Figure 16: Disease- modifying therapies (DMTs) for the prolonged treatment of MS.
Source: Author's elaboration.

More accurately, in reference to the specific disease-modifying therapies (DMTs) that each patient received, Figure 17 can be carefully observed. The beginning of the x-axis represents the debut of the DMT for each individual patient and the y-axis represents the years during which each type of disease-modifying therapy (DMT) was being administered.

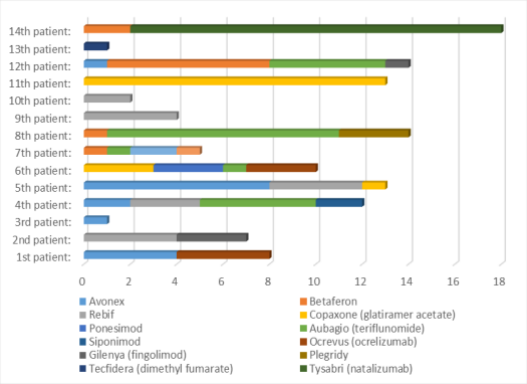

Figure 17: Disease- modifying therapies (DMTs) as a prolonged treatment of EOMS.
Source: Author's elaboration.

Furthermore, concerning the plausible side effects of the various disease-modifying therapies (DMTs) in each patient with multiple sclerosis and the most recent evaluation of their prognosis, Figures 18 and 19 can be observed.

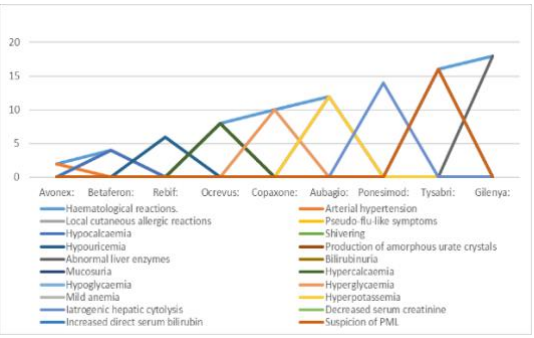

Figure 18: Plausible side effects of the various Disease-Modifying Therapies (DMTs)
Source: Author's elaboration.

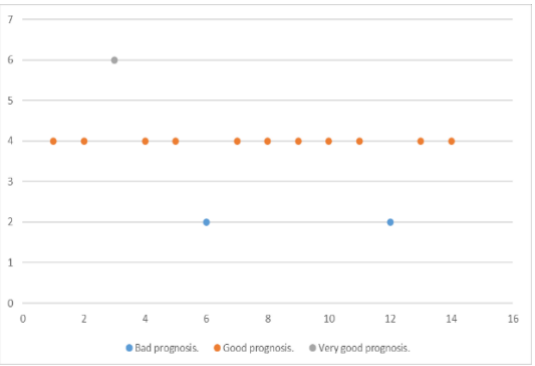

Figure 19: Recent DMT vs. Prognosis
Source: Author's elaboration.

4. DISCUSSION

For the successful diagnosis of a suspected case of multiple sclerosis, Magnetic Resonance Imaging (MRI) is the paraclinical examination of choice [1,19]. This specific imagistic technique has a very high sensitivity of 87% and a specificity of 73% [1]. In a typical case of multiple sclerosis, focal and well- demarcated brain MRI lesions are located in particular areas of the white matter [1,2]. For instance, they are localised in the periventricular, the cortical and juxtacortical anatomical regions, the corpus callosum, the pons and the cerebellum, which constitute the infratentorial regions, and in the cervical segments of the spinal cord [1,2,19]. The demyelinating plaques seen in MRI frequently appear to be ovoid [1,19].

'Dawson fingers' are considered to be a pathognomonic sign of multiple sclerosis [1,19]. On a sagittal view in MRI, several periventricular lesions are distributed at characteristic right angles towards the corpus callosum, thus giving the impression that they originate and radiate from this area [1,19]. On proton- density and T2-weighted MRI, the lesions tend to present as hyperintense [1,19]. On the contrary, in T1- weighted images especially of an old case of multiple sclerosis, the same lesions appear as hypointense, being named 'black holes', or a group of them cannot even be seen at all [1,19].

Children with suspected multiple sclerosis should mandatorily undergo both a gadolinium-enhanced and a non-contrast-enhanced MRI paraclinical investigation [2]. In every patient being diagnosed with an acquired demyelinating syndrome, a brain MRI will be proven very helpful in assessing the risk of developing MS [2]. In case of any clinical manifestations indicating the involvement of the spinal cord or if there is an inconclusive brain- MRI outcome, then a complete spinal cord MRI should be performed [2].

Simultaneously, a specific MRI of the optic nerve is useful to be suggested in patients with suspected MS, when there is a differential diagnosis of neuromyelitis optica spectrum disorders (NMOSD) or a myelin oligodendrocyte glycoprotein antibody- associated disease (MOGAD) to be excluded [2]. Specifically, T2 fluid- attenuated inversion recovery image sequences (FLAIR) are considered to be the most sensitive type, in order to evaluate especially the periventricular lesions [2].

Nowadays, MRI is considered to be an extremely useful tool not only for the actual diagnosis of multiple sclerosis, but also for the confirmation and monitoring of the disease's progression in the central nervous system (CNS) throughout the years, its prognosis and treatment [23,24]. Generally, radiography as another imagistic technique

has a limited appliance in diagnosing patients with MS and it is most commonly used, in order to exclude mechanical bony lesions [4].

According to the new guidelines, standardized MRI paraclinical investigations and gadolinium-enhancing contrast agents can be used not only in adults, but also in children and pregnant women [24]. Three- dimensional MRI techniques are preferred opposed to the two- dimensional ones, when they are available [24]. More precisely, the sagittal 3-D T2-weighted fluid-attenuated inversion recovery (FLAIR) is considered to be the best choice due to its considerably higher sensitivity [24].

During the execution of this retrospective clinical study, the majority of patients, except for merely one paediatric patient, had no active lesions in their last MRI paraclinical investigation. These were non-gadolinophilic lesions in the contrast-enhanced MRI, with a stationary aspect and no changes considering their dimensions. On the contrary, only one out of these fourteen patients had a progression of multiple sclerosis even on their last MRI investigation, with one active gadolinophilic lesion.

In the following two clinical cases (Images 1-4), there can be observed the MRI findings of one former, meaning an image taken early-on during the course of this demyelinating disease, and one more recent paraclinical investigation of two non-specific patients with multiple sclerosis. In the case of the third non-specific patient (Images 5-8), the article presents the data of the patient's recent MRI findings.

5. CONCLUSION

5.1. Epidemiology

The retrospective observational clinical study presented an equal gender representation of an Early-onset multiple sclerosis (EOMS) with a female-to-male ratio 1:1. In reference to the bibliography [2], multiple sclerosis typically manifests in female patients, being older than 12 years and younger than 18 years of age, more frequently than in their male peers, with an approximate female-to-male ratio 2.8. However, due to the limited number of patients having participated in the clinical study, no difference in the female-to-male ratio of patients with multiple sclerosis can be assessed between the data of this preliminary study and the literature.

Regarding the age of the initial clinical presentation of EOMS, only one out of these fourteen patients was younger than 10 years old. More precisely, this patient was 8 years old, thus being in accordance with the literature [2], where it is stated that the manifestation of EOMS accounts for less than 1% before the age of 10 years.

5.2. Pathogenesis and environmental triggers

The clinical study identified the Cytomegalovirus (CMV) as a possible etiologic factor of MS and not as a protective factor, as being stated in various other scientific articles [5]. However, the deficiency of the 25-hydroxyl-vitamin D of the sunlight was also identified as a causative agent of multiple sclerosis in the clinical study, in accordance to the bibliography [5].

5.3. Clinical phenotypes and features

Three out of these 14 patients initially presented with a Clinically- isolated syndrome (CIS), being progressed into Relapsing-Remitting Multiple Sclerosis (RRMS) after their second MS attack. This fact proves the original statement from the literature that the CIS manifests more commonly in paediatric patients with an EOMS [2]. The majority of the patients in this clinical study initially presented with RRMS, which is also in accordance with the literature stating that RRMS is the primary clinical form for (97-99) % of the affected paediatric population [2].

In addition, the clinical study showed that fatigue was generally associated with depression and a worse evolution of the disease in the paediatric patients [2]. In agreement with the literature [2], the clinical study indicated that cognitive impairment can also affect the paediatric patients with multiple sclerosis and it can vary according to the duration and the intensity of the respective MS attack. Simultaneously, many patients were identified in this clinical study who presented with language disorders and concentration difficulties during the course of their disease [2].

5.4. Course

As literature has underlined [30] the fact that the paediatric patients with EOMS have a higher risk of developing numerous acute relapses of MS, the clinical study has confirmed that the majority of the included patients had presented more than three neurological episodes in total. The clinical study also showed congruent results, proving the statement that even though the paediatric patients are more likely to have a slower progression of multiple sclerosis, they ultimately suffer from significant neurological deterioration at an earlier age [30]. Therefore, the neurological clinical manifestation of multiple sclerosis has a more significant impact on the paediatric patients than on the adult ones [30]. More precisely, these fourteen paediatric patients experienced a variety of clinical manifestations, mainly motor deficits.

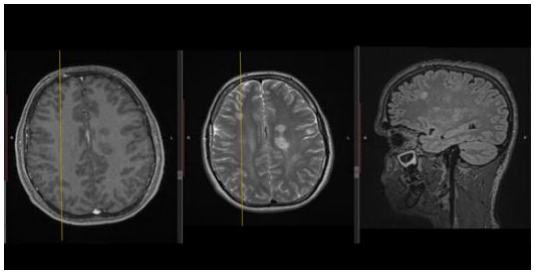

Image 1: First non-specific patient, former MRI**.** *T1- contrast- enhanced (left image) and T1-native (middle image) cerebral MRI images: black holes can be observed, depicting the degenerative process of multiple sclerosis.* Source: Author's elaboration.

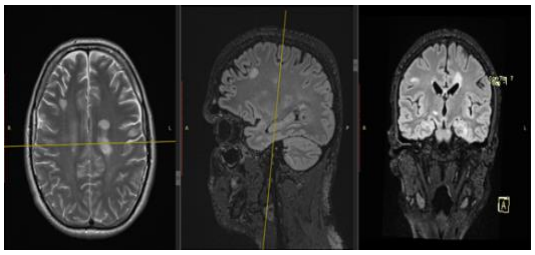

Image 2: First non-specific patient, recent MRI. *Multiple, cerebral, demyelinating, inflammatory lesions, suggestive of multiple sclerosis.* Source: Author's elaboration

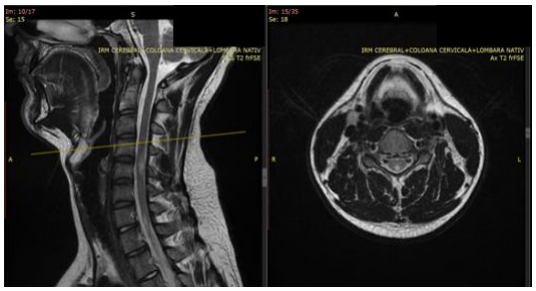

Image 3: Second non-specific patient, former MRI. *Multiple, medullary, demyelinating lesions of the cerebellum, brainstem and cervico-thoracic spinal cord.* Source: Author's elaboration.

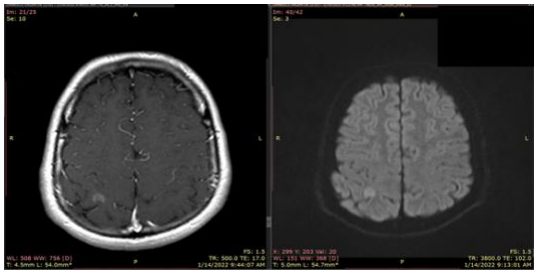

Image 4: Second non-specific patient, recent MRI. *Multiple, active, cerebral, demyelinating lesions in diffusion and contrast-enhanced Magnetic-Resonance Imaging.* Source: Author's elaboration.

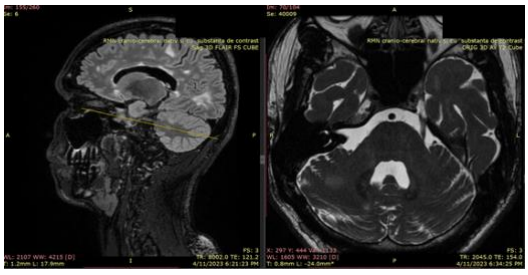

Image 5: Third non-specific patient, recent MRI. *Multiple typical MS lesions at the supratentorial & infratentorial level - periventricular, subcortical and cerebellar white matter. Active, contrast-enhanced cerebral lesions.* Source: Author's elaboration.

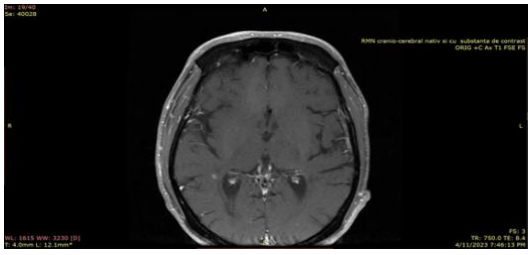

Image 6: Third non-specific patient, recent MRI. *Multiple typical MS lesions at the supratentorial level – periventricular and subcortical. Active, contrast-enhanced cerebral lesions.* Source: Author's elaboration.

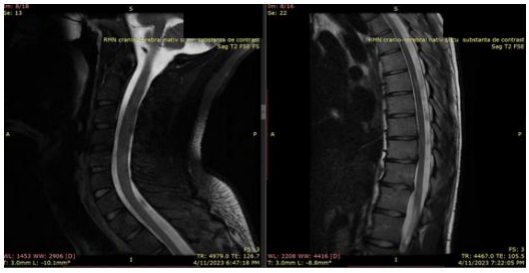

Image 7: Third non-specific patient, recent MRI. *Multiple, active, contrast-enhanced, demyelinating lesions of the thoracic spinal cord.* Source: Author's elaboration.

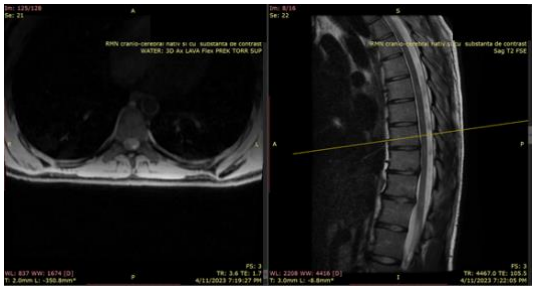

Image 8: Third non-specific patient, recent MRI. *Spinal cord lesions- typically a short segment involved- less than 2 segments. It is typical for MS, the respective segment to be triangular in shape & mostly located dorsally or laterally.* Source: Author's elaboration.

5.5. Diagnostic criteria

According to the clinical study, all the paediatric patients were ultimately diagnosed with multiple sclerosis, by fulfilling all the McDonald diagnostic criteria with dissemination of the lesions in time and space [1]. Additionally, thirteen out of these fourteen patients had no active lesions during their last MRI paraclinical investigation, after receiving treatment with at least one DMT. Therefore, this fact proved the statement in the bibliography that paediatric patients with MS have a better probability of recovery, with an increased likelihood of the lesions to get reversed on follow-up MRI imaging [2].

5.6. Treatment

The clinical study verified the data obtained in the literature [14] regarding the treatment of multiple sclerosis.

On the one hand, concerning the treatment of an acute MS exacerbation, the aforementioned paediatric patients were mainly being treated with a high-dose of glucocorticoids. More precisely, with methylprednisolone (Solumedrol), prednisone or rarely, specifically in the case of one paediatric patient, with dexamethasone.

On the other hand, for the prolonged treatment of multiple sclerosis, disease-modifying therapies (DMTs) were mostly preferred [14]. During the aforementioned clinical study, older injectable platform DMTs, such as interferons beta-1a (Avonex, Rebif), were mainly used for the treatment of paediatric patients who had a mild-to-moderate MS with minimal functional deterioration.

In case of treatment failure, for the treatment of refractory MS, the paediatric patients who had a poor response to interferon beta drugs (Avonex, Rebif), switched their therapy into an oral DMT with intermediate efficacy, such as fingolimod (Gilenya) or ocrelizumab (Ocrevus). In a similar manner, when a paediatric patient had a poor response to interferons beta-1a (Avonex, Rebif) and even presented some associated adverse reactions, for instance hematological adverse reactions or shivering respectively, then their treatment was alternated into either a higher-dose of another interferon-beta medication or to ocrelizumab (Ocrevus), fingolimod (Gilenya), teriflunomide (Aubagio) or glatiramer acetate (Copaxone).

According to the literature [30], many paediatric patients presented a variety of adverse reactions during their treatment with DMTs. For instance, some children being treated with interferon beta-1b (Betaferon) presented local allergic reactions at the site of the injection and pseudo-flu-like symptoms, whereas a patient being treated with interferon beta-1a (Rebif) presented shivering. Also, various hematological adverse reactions manifested in paediatric patients being under treatment with ocrelizumab (Ocrevus), fingolimod (Gilenya), interferon beta-1a (Avonex), glatiramer acetate (Copaxone), interferon beta-1b (Betaferon), teriflunomide (Aubagio) and natalizumab (Tysabri). An iatrogenic hepatic cytolysis was even caused in a patient being treated with ponesimod.

In conclusion, the presented article emphasizes that the entire treatment of multiple sclerosis requires a team approach with a psychologist and a psychiatrist working together with these patients, who are no more children or adolescents and they have actually become real adults, with all the included social challenges.

5.7. Prognosis

In reference to the bibliography [30] concerning the paediatric patients with multiple sclerosis, an increased relapse rate within the first two years from the initiation of this demyelinating disorder and a progressive course at the level of its onset can contribute as negative prognostic factors. Nevertheless, paediatric patients with an Early-onset multiple sclerosis (EOMS) can have a more promising and better prognosis, when they are being treated by various disease-modifying therapies (DMTs) [30].

These data were verified during the execution of the aforementioned clinical study. Most importantly, it was underlined that the appearance of epileptic seizures, a cerebellar and a vestibular syndrome can contribute as negative prognostic factors to multiple sclerosis. More precisely, even though epilepsy is an unusual and uncommon feature of multiple sclerosis leading to a significant deterioration of the clinical status of the patient [16, 30], one out of the aforementioned fourteen patients presented with general tonic-clonic seizures during the clinical study.

5.8. Pregnancy

During the aforementioned clinical study, it was verified from the data in the literature [16] that pregnancy actually plays a protective role against the manifestation of multiple sclerosis, having a decreasing effect in the rate of MS exacerbations. More specifically, one pregnant female patient with multiple sclerosis was retrospectively evaluated during this study. It was underlined that, even if the patient had experienced numerous MS exacerbations and had a bad evolution of her disease before pregnancy, during her pregnancy she did not have

any new neurological episodes instead, thus manifesting a good prognosis.

Finally, although this preliminary study focuses on a limited number of cases with multiple sclerosis, it describes its evolution from paediatric patients into adulthood in an analytical manner. Most importantly, this article presents a specific case, where the patient with multiple sclerosis also suffers from general epileptic seizures- an unusual manifestation of this demyelinating disease. Simultaneously, it questions the hypothesis derived from the literature data that the Cytomegalovirus (CMV) is a protective agent of multiple sclerosis and emphasizes the possibility of this specific virus to be a causative agent instead. Therefore, it is suggested for the presented article to be used as a reference point for future studies.

AVAILABILITY OF DATA AND MATERIALS

The datasets generated and/or analysed during the current study are not publicly available due to the confidentiality of the clinical data, but they are available from the corresponding author on reasonable request.

ETHICS AND PARTICIPATION CONSENT

The present study was approved by the Neurological Scientific Committee of the 'Emergency University Hospital of Bucharest' (SUUB).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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