

MULTIPLE SCLEROSIS IN CHILDREN: A REVIEW OF CLINICAL AND PARA CLINICAL FEATURES IN 26 CASES

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Abstract

Objective

Multiple sclerosis (MS) is an inflammatory demyelinating disease of central nervous system (CNS) that is increasingly being recognized as a disease affecting children. However, the clinical features of childhood MS at onset have been rarely reported from Asia.

Materials & Methods

This report presents a retrospective chart review of 26 patients with MS (20 females and 6 males), with an onset age of MS of less than 16 years, in the south of Iran between March 2001 and November 2007; it documents researchers' experiences

Results

Female/male ratio was 3:1. Mean age in females was higher than males (13 vs.12.16). The disease was highly variable in onset presentation; the most common initial symptoms were limb weakness, disequilibrium, and diplopia. Three patients had a positive family history of MS in their first degree relatives. VEP was abnormal in 9 of 19(47%). MRI demonstrated multiple plaques in the brain in 24(92%) cases. Relapse remitting MS was a dominant pattern noticed in 23(88%) cases.

Conclusion

MS, in childhood, is not as rare as commonly believed; although its diagnosis is essentially a clinical one, paraclinical investigations are of great value in the identification of demyelinating disorders in childhood. The disease, as it occurs in children, does not appear to differ clinically from the disease as observed in adults. If pediatricians should confront a child showing evidence of scattered neurological deficits that remit, particularly weakness, disturbance of vision and co-ordination, they need to consider the possibility of MS.

Keywords: Multiple sclerosis, Children, Demyelinating Disease, Magnetic Resonance Imaging (MRI)

Introduction

Multiple sclerosis (MS) is a chronic autoimmune inflammatory demyelinating disease of central nervous system (CNS) that is increasingly being recognized as a disease affecting children (1). The occurrence of MS in children has been the subject of recurring discussions for over 80 years (2); the controversy that existed at the beginning of 20th century on the possibility that the MS occurs in childhood probably arose because MS is primarily a disease of young adulthood with a clinical

onset usually occurring between 20 and 40 years of age (3,4). Numerous studies indicate an average age at onset of 30 years, but the span is considerable and diagnostic criteria now include the possibility that the disease may become manifest between the ages of 10 and 59 years (4,5). Even so, clinical onset at an earlier (or later) age is no reason to exclude the diagnosis of MS; however, in 3 to 5% of cases, MS begins before the age of 15 (5). McAlpine, combined data from a number of studies from various countries (5700 patients) and showed that incidence of MS before age 10 years was less than 3 per 1000 (6). Muller reported of 810 cases from Sweden and noted that in 46 patients (5.6%), the onset was before 15 years of age (7). The youngest known patient with MS yet described was a 24 month old child (8). Hauser et al. reported a child with onset of MS at 2 years of age (9) and Di Mario et al. presented a 4 year-old child with MS and typical clinical and nuclear magnetic resonance imaging(MRI) correlations (10). As onset of this disease can be delayed till 60s and 70s. There are very few disease with such a wide range of onset.

Since the clinical features of childhood MS at onset in Asia have been rarely reported, and there is a lack of awareness among pediatricians as to the occurrence of MS in children; our intention was to review our own observations of clinical and paraclinical features in patients whose symptoms started before 16 years of age (11). Most frequently a meticulous, time consuming and costly search for metabolic and degenerative disorders is initiated before the diagnosis of MS is considered, leading to a significant diagnostic and therapeutic delay in many young patients.

Materials & Methods

This report presents researchers' experience using a retrospective chart review of 26 patients with MS (20 females and 6 males) with onset age before 16 years (mean age of 11.8 +/-2.7 years), admitted to the Nemazee hospital, a referred hospital in south of Iran in Fars province, Shiraz, between March 2001 and November 2007 and can thus be considered as representative of MS occurring in childhood. Particular attention was given to exclude other diseases such as post infectious encephalomyelitis, acute disseminated encephalomyelitis, vasculitis and other demyelinating disorders. As a consequence,

questionable or borderline cases were excluded. Data analyzed were sex and age distribution at onset, initial symptoms, symptoms occurring in the course of illness, physical findings, family history, clinical course, rate of relapses, cerebrospinal fluid (CSF) analysis result, magnetic resonance imaging (MRI) result, visual evoke potential (VEP) result, other laboratory studies and the treatments applied. All patients had clinically been defined as MS according to Poser's criteria (12), viz. a history of two attacks and clinical evidence of two separate lesions or two attacks, clinical evidence of one lesion and paraclinical evidence of another, separate lesion (4). Family history was considered positive if a first or second degree relative was reported or known to have MS. Statistical analysis was performed by statistical software SSPS version 9 after encoding and got entering to computer and necessary information was obtained.

Results

Age and Sex Distribution

Of a group of 26 patients, 20 were girls (76%) and 6 boys (24%); female/male ratio was 3:1. Significant sex related differences in the symptoms, signs, or course of the disease were not noted. Age at the onset of the neurological symptoms ranged from 6 to 16 years. The two youngest patients were aged 6 and 8 years, both males, while the three youngest female patients were aged 9. The mean age at onset was 11.8 years. The mean age in females was higher than in males (13.2 vs. 12.3). Nineteen (76%) of the patients were aged over 12 years.

Symptoms at Onset

The disease was highly variable in presentation at onset. In the majority of cases physical symptoms were not present at onset of disease; the patient simply became aware of the gradual or sudden appearance of an impairment of neurologic function. In 17 patients (65%), mode of onset was rapid or with sudden appearance within a few days, especially when visual symptoms were the initial chief complaint; in 9 cases (36%) however, the development of initial symptoms mainly weakness in a limb occurred so gradually that no definite date of onset could be determined. In five cases, the initial episode was accompanied by one or more of the following

symptoms: mild headache in 3, nausea and vomiting in 4, drowsiness in 3 and dysequilibrium (dizziness or true vertigo) in 2 and fever in one case.

The initial clinical manifestations, in decreasing order of frequency were limb weakness in 19 cases (73%), diplopia in 8 (30%), ataxia or incoordination in 8 (27%), blurred vision in 6 (23%), sensation loss in 5 (19%) and sphincter problems in one case (4%).

Symptoms occurring within study period

Symptoms seen during the clinical course of illness, in order of decreasing frequency were: limb weakness in 21 cases (80%), sensation loss in 16 (61%), ataxia and incoordination in 14 (53%), blurred vision in 13 (50%), diplopia in 9 (34%), nystagmus in 4 (15%), sphincter problems in 4 (15%), facial palsy in 3 (11%), limb neglect in one (4%), seizure in one (4%), emotional stress attacks in one (4%) and confusion in one case (4%).

In one patient (4%) episodes suggesting convulsion occurred, apparently they were not associated with any other neurologic deficit at the time of the seizure.

Physical Findings

Muscle weakness was observed in 21 cases (84%); both legs were involved in 15 cases (60%) one leg in 5 (20%), both arms in cases (44%) and one arm in 8 (32%) cases. Ataxic gait and incoordination was observed in 8 cases (30.7%). Babinski's reflex was present in 5 cases (25%). Hyper-reflexia was seen in deep tendon reflexes (DTR) of 10 cases (40%). Hypo-reflexia was seen in DTRs of 4 cases (16%).

Fourteen patients (56) exhibited abnormalities of visual apparatus. Optic neuritis was present in 5 patients (20%) and optic atrophy was present in 3 patients (12%), of which one patient had previous attack of optic neuritis that had not been recognized and had recently presented with motor symptoms, with optic atrophy being detected incidentally. Facial palsy was seen in 3 cases (12%). Impaired gag reflex (cranial nerve IX) was seen in two cases (8%). Right V and VI cranial nerve palsy was seen in 2 patients (8%). Impairment of cranial nerves X and XII was seen in one patient (4%).

Sensory level was found in 4 patients (16%). Romberg's and Hoffmann's sign was observed to be positive in

2 patients (8%). Lhermitte's sign was observed to be positive in two patients (7.6%).

Disatometamyelia and diabetes mellitus was seen in one patient each.

Three patients had a positive family history of MS in first degree relatives. Other family histories were: migraine headaches, cerebral palsy, and diabetes mellitus in one patient each.

Twenty-three patients (88%) had a relapsing and remitting disease, two patients had primary progressive disease (7%) and one patient had chronic progressive disease (4%). Over all the mean rate of relapses/year was 0.50 per year.

A fifteen year-old female patient who had the primary progressive pattern of the disease, became handicapped and bed-ridden and attempted suicide due to deep depression; she died due to aspiration pneumonia and sepsis because of multiple deep bed-sores, resulting in cardiopulmonary arrest; the relapse rate for this patient was 1.25 per year. Another nine year-old female patient, also with the primary progressive pattern of the disease, also became handicapped, completely dependent on others for walking; follow up data was not available for this patient and the relapse rate for this patient was 1 per year. Another 15 year-old female patient with the chronic progressive pattern of the disease developed weakness, ataxia and optic neuritis with increasing frequency of attacks over five years; however this did not lead to any severe disability within the study period; relapse rate for this patient was 0.6 per year.

Laboratory studies on cerebrospinal fluid were performed in all the patients. The fluid was normal in only one instance (proteins, cell counts). The specimens in these cases contained one to 24 leukocytes and had one to 11 lymphocytes. The fluid from 6 patients (23%) contained abnormal amounts of protein concentrations, over 40 mg/100 ml. The IgG levels in CSF were available for 2 patients, normal in one and high in the other. Electrophoresis was available for only 3 patients, being abnormal in one patient. Vasculitis work ups, such as Anti Nuclear Antibody (ANA), Double strand DNA, Anti-Neutrophil Cytoplasmic Antibody (ANCA), Anti-Cardiolipin Antibody (ACLA), C3, C4 was done in 17 patients (68%), being positive in one patient; a repeat of the test, gave normal results. Serum was checked for

anti smooth muscle antibody in one patient, human T-lymphocyte virus 1 (HTLV1) antibody in one patient, VDRL in one patient, proC and proA in one patient (4%) and all results were negative. Folic acid and Vit B levels in serum were checked in one patient and were normal. The patients had no clinical finding of vasculitis.

Brain MRIs, using the T2 and T1 techniques with or without contrast were performed in all the patients (100%). All plaques were detected as multiple hypersignal areas of white matter in T2 and hyposignal in T1 which were disseminated in space. The most common sites involved in order of decreasing frequency are seen in figure 1.

Visual evoke potential was done in 19 cases (76%) and was abnormal with prolonged latency in 9 cases (48%). Bilateral impaired VEP was seen in 6 cases (31%). In 4 cases who had bilateral prolong latency, normal fundoscopy was found.

Treatments prescribed for acute attacks of MS, in order of decreasing frequency, were methylprednisolone in 20 patients (76%), dexamethazone in 4 patients (15%) and IV IG in two patients (7%), plasmaphoresis in one patient (4%). After treatment of acute attack, prophylaxis for prevention recurrence of attack was used in 9 patients. INF-B 1a (Avonex) injection was administered in 8 patients (30%) and Rebif was used in one patient (4%) because the response to Avonex injection was not good and weakness had developed.

Discussion

We have presented the clinical and paraclinical data of 26 patients with MS, with an onset of disease before 16 years of age; the results can thus be considered as representative of MS in childhood from the region studied.

The prevalence of multiple sclerosis (MS) worldwide shows considerable variability. According to Kurtzke, Iran is considered to have a low prevalence. Kalanie H& et al reviewed 200 cases of MS in Tehran (13) Etemadifar M& et al showed that Isfahan (a big city in center of Iran) could be considered as an area with a medium to high risk of MS. [14]. A 3-year study, done by Ghofrani M& et al (1998 to 2001) on twenty patients, in the Mofid pediatric hospital, Tehran has tried to describe the disease according to clinical, electrodiagnosical and

neuro-imaging (15).

As known, MS is more common in women than in men; the sex ratio ranges between 1.9: 1 and 3. 1: 1, being 3: 1 in our study. An increase in the female to male ratio in childhood cases has also been demonstrated in previous studies by Dequette & et al in 1987 (16) and Hanefeld in 1993 (17). MS is an autoimmune disease and differences in sex ratios are the rule in autoimmune diseases (18). Sex hormones influence immunity, probably by acting on the thymus gland or on the T-lymphocyte subset. Female predominance may suggest a role of hormonal changes in puberty in triggering MS onset, possibly by an influence on T-lymphocyte subsets (18,19).

The disease as it occurs in children does not appear to differ clinically from the disease observed in adults regarding the mode of onset, symptoms and physical findings. Just as in adults, evidence of weakness of limbs, incoordination, and visual disturbance and so on are present in the majority of instances seen among children (2).

In our study, the initial clinical manifestations were motor disturbances, diplopia, ataxia or incoordination. In their multicenter study of 125 patients with childhood MS, Duquette, et al (16) reported that sensory disturbances were the most common initial manifestation of disease, occurring in 26.4% of cases, followed by optic neuritis (14%), motor disturbances (11%), diplopia (11%), gait problems (8%) and cerebellar ataxia (5%). Among 149 MS patients, with onset of disease before the age of 16 years, Ghezzi & et al (20) found that brainstem dysfunction (25%), as an initial symptom, was more frequent compared to other systems and onset of adult MS symptoms. In a recent study, Ruggieri & et al (21) found that ataxia was preponderant as an initial symptom in the group of childhood MS cases with onset before 15 years of age. In that study, optic nerve involvement became more frequent with progressive age (21); in this age group, the disease was initiated by weakness, visual or sensory symptoms that would frequently remit completely and usually evolved in a relapsing remitting manner, although the course was initially progressive in some patients. The clinical course of childhood MS in literature (16,22,23) points out the preponderance of relapsing-remitting form ranging from 56 to 62.5% compared with our series (88%). In the same studies,

secondary progressive and primary progressive forms were reported in 22% and 25% of patients, respectively. In our study, two patients had primary progressive disease and one patient had chronic progressive disease (24).

In their multicenter study of 125 patients with childhood MS, Duquette & et al (16) reported a 21% prevalence of positive family history of MS. Our result with the prevalence of 11.5% was lower than that of the Duquette et al study and other previously reported studies (25).

MRI has demonstrated complete accuracy in defining MS plaques in adult onset MS. In our study, 100% of patients revealed characteristic abnormalities consistent with those lesions differentiated by MRI among adults; MRI therefore, seems to be a valuable diagnostic procedure in children as well as in adults. The same results can be seen in Sindern's study, who observed characteristic MRI findings in 23 of 28 juvenile patients (16). In another study, Selcen & et al (26) reviewed 16 patients diagnosed as having MS before the age of 17 and they found that MRI was positive in 80% of patients.

Pohl & et al evaluated multimodal evoked potentials in pediatric patients with MS and showed abnormal EP in 82% of the children. Our evaluation of evoked potentials showed abnormal EP in 70% of the children (27).

In our study, 23% of CSFs contained abnormal amounts of protein concentration over 40 mg/100 ml. Between 40 to 90% of pediatric MS patients were reported to have increased intrathecal IgG synthesis, or production of myelin basic protein, or oligoclonal bands (OCB) in CSF. A retrospective analysis of 136 patients with MS with disease onset < 16 years showed that 92% had either an increased IgG index or OCB, with a sensitivity similar to that observed in the adults (8).

In conclusion, clinical and demographic characteristics of our patients were similar to other reports; however, some differences existed.

The data presented indicate that from a clinical standpoint, multiple sclerosis does occur in children and is not so rare in childhood and although its diagnosis is essentially a clinical one, paraclinical investigations are of great value in the identification of demyelinating disorders in childhood.

Should a pediatrician encounter a child showing evidence of scattered neurological deficits that remit, particularly

weakness, disturbance of vision and coordination, he or she should consider the possibility of MS. The possibility of other diseases also must be considered carefully. If specific treatment of MS becomes available, however, early diagnosis would appear to be important.

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