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Severe myoclonic epilepsy in infancy: evolution of seizures

T. OHKI, K. WATANABE, T. NEGORO, K. ASO, Y. HAGA, K. KASAI, M. KITO & N. MAEDA

Department of Pediatrics, Nagoya University School of Medicine, Nagoya, Japan

Changes in seizure type of severe myoclonic epilepsy (SME) in infancy were reviewed retrospectively in 14 patients (11 males and 3 females) who were followed-up to the age of 7 years or more. The observation period ranged from 5 to 16 years with a mean of 10 years. During the follow-up, three or four types of seizures were seen per patient, but the pattern of appearance and disappearance of each seizure type varied considerably among the patients. Tonic–clonic convulsion, either generalized or unilateral, was seen most consistently through the entire course, and it continued to the end of follow-up in 11 patients (79%). On the contrary, myoclonic seizure, complex partial seizure, and atypical absence often disappeared and reappeared repeatedly during the course. In SME, seizure symptoms varied widely among patients in comparison with other neurological symptoms, and the most consistent core seizure type was tonic–clonic convulsions.

Key words: severe myoclonic epilepsy; infancy; long-term follow-up; status epilepticus; photosensitivity.

INTRODUCTION

Severe myoclonic epilepsy (SME) in infancy exhibits various types of seizure during its course. However, there have been few reports on the long-term evolution of seizures in this epileptic syndrome. We analysed retrospectively changes in the seizure type in 14 SME patients.

SUBJECTS AND METHODS

The subjects were 14 patients (11 male and three female) who fulfilled the following conditions: (1) no neurological sign prior to the onset of epilepsy and no neuroimaging investigation indicating organic brain lesions; (2) gradual appearance of psychomotor retardation after onset of epilepsy; (3) intractable tonic–clonic convulsions, either generalized or unilateral, which tended to prolong and occur in clusters; (4) existence of myoclonic seizures during the course; and (5) follow-up to the age of 7 years or more. The age at the initial examination was 5 months to 2 years 8 months (mean 1 year 5 months). The duration of follow-up ranged from 5 to 17 years (mean 11 years). During the observation period, electroencephalography (EEG) was performed at least once a year. We tried to identify the types of seizure by simultaneous VTR-EEG recording. If not, the types of seizure were identified with inter-ictal EEGs, observed seizure manifestations and the families' observations of seizure manifestations, number of seizures and the time of their occurrence. Seizures were classified according to the international seizure classification of 1981[1]. However, generalized or unilateral dominant tonic–clonic convulsions were together regarded as generalized motor seizure (GMS) in this study.

RESULTS

Review of family history revealed convulsive disorders in the relatives of the third degree in 10 patients (71%): febrile convulsion in five and epilepsy in five. Of the five patients with a familial history of epilepsy, two were male identical twins. The psychomotor development was normal in all patients prior to the onset of epilepsy, but retardation became apparent at the age of 1–2. The patients began to walk at the mean age of 14 months, and all became capable of ambulation. However, nine patients showed very unstable gait with the hips thrust backwards and upper limbs bent and five patients trembled the fingers during motion. At the end of the follow-up, four uttered several words and three of them could speak two-word sentences, but verbal communication was very poor and none could make a conversa-

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tion. After the age of 3 years, however, none of the patients showed progressive psychomotor regression. Computed tomography (CT) was performed in all patients, and no abnormality was noted except one patient who had an arachinoid cyst below the left temporal lobe. Magnetic resonance imaging (MRI) was done in six patients, and no morphological abnormality was noted in any of them.

The age at the onset of epilepsy ranged from 2 to 10 months (mean 6 months). Figure 1 shows changes in the seizure type in each patient. Throughout the follow-up period, all 14 patients had myoclonic seizure (MS), GMS, and complex partial seizure (CPS), and 13 had atypical absence (AA). The appearance, continuation, and disappearance of seizure types was similar in the identical twins (cases 9 and 10). On the contrary, the remaining 12 patients showed no common pattern in the appearance, continuation, or disappearance of each seizure types except for GMS which persisted over nearly the entire follow-up period in most patients.

The seizure type at the onset of epilepsy was

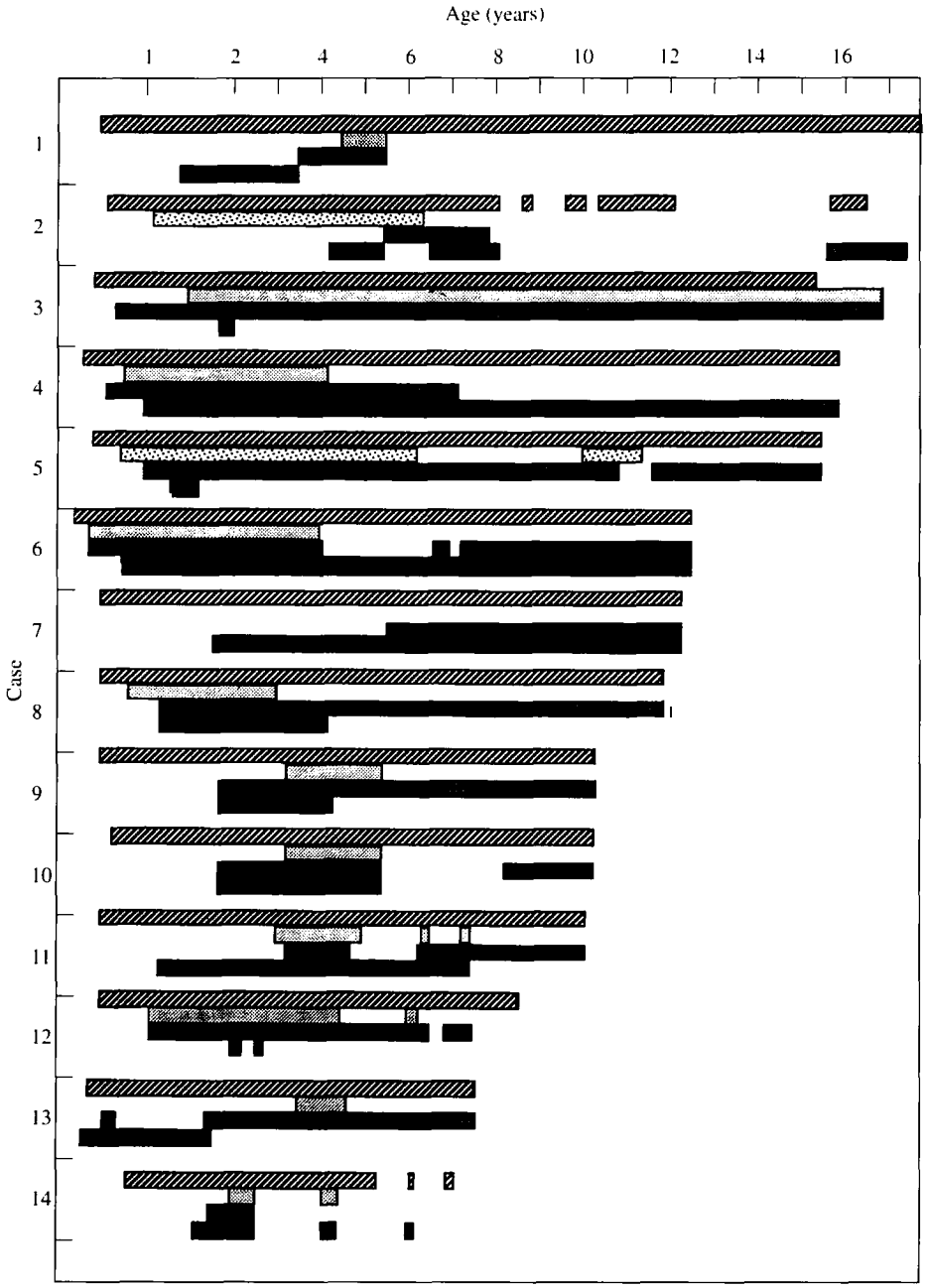

Fig. 1: Changes in the seizure type in each patient. ▨, generalized motor seizures; □, atypical absences; ■, myoclonic seizures; □, complex partial seizures.

GMS in 13 patients and complex partial seizures (CPS) in one. The initial seizure was accompanied by fever in 10 patients, and the fever was moderate (<38.5°C) in six of them. In these 10 patients, afebrile convulsion occurred 2–14 months (mean 5 months) after the onset. Of four patients in whom the initial seizures was afebrile, two had the initial seizures during or immediately after taking a bath. Including these two patients, 12 (86%) had GMS or CPS when taking a bath throughout the follow-up, especially in infancy. At the onset of epilepsy, seizures prolonged for more than 20 minutes in five patients and occurred in clusters in one. The other eight patients also had prolonged or clustering seizures 1–13 months (mean 6 months) after the onset of epilepsy. The seizure type that occurred next to the first was GMS in one patient, MS in two, CPS in four, and AA in three. As the second seizure type, MS and AA occurred nearly simultaneously in two patients, and MS and CPS in other two patients. The duration between the first and second seizure type ranged from 1 to 16 months (mean 8 months). The third seizure type was MS in six, CPS in one, AA in two (four patients in whom two seizure types appeared nearly simultaneously as the second seizure type were excluded). MS and CPS appeared nearly simultaneously in one patient.

MS was seen, by definition, in all patients, appearing at the age of 4 months to 5 years 7 months (mean 2 years 2 months). MS appeared before the age of 4 years in 12 patients. In the remaining two patients, the first MS developed at the age of 5 years 6 months and 5 years 7 months. Of these two patients, one had a seizure free period during the course and the other had no AA. At the end of the follow-up, nine patients still had MS. Four of them continued to have MS from the onset of this seizure, but in the remaining five patients, MS disappeared once and recurred after a latency of 2 months to 2 years 11 months (mean 1 year 6 months). In the other five patients, MS appeared temporarily during the course but was absent at the end of the follow-up. The frequency of MS tended to decrease with age even in those who continued to have this seizure until the end of the observation period. MS were primarily massive myoclonus, but MS localized in the face, upper limbs, or lower limbs or unilateral MS occurred in eight patients. Seizures varied in intensity from violent ones that made the patient fall to very mild ones that were perceived only by the mother holding the child. Ictal EEGs were recorded 80 times in seven patients. Generalized spike and wave complex accompanied seizures in all records (Fig. 2), and there was no correlation between EEG pattern and the intensity or the site of the seizure.

Thirteen (93%) of the 14 patients had AA. The pattern of its appearance also differed widely among the patients. The age at the appearance of AA ranged from 4 months to 6 years (mean 2 years). One patient continued to have AA until the end of the follow up, but it disappeared before the age of 7 years in eight. In the remaining four patients, AA disappeared once but recurred after a latency of 1–3 years (mean 2 years). In one of them, AA repeated appearance and disappearance several times. Similarly to MS, frequency of AA tended to decrease after the age of 7 years even in patients who continued to have AA until the end of the observation period. Ictal EEGs of AA were recorded 14 times in three patients. The EEG showed generalized irregular spike waves in association with the seizures (Fig. 3). Duration of these seizures was short, continuing for <10 s.

All 14 patients had CPS. It consisted mainly of eye deviation, cyanosis, and partial motor symptoms. Marked automatism was noted in only one patient. The age at the appearance of CPS was 4 months to 4 years (mean 1 year 7 months). In 13 (93%) patients, CPS developed at the age of <2 years. Three patients continued to have CPS from the onset to the end of the observation period. On

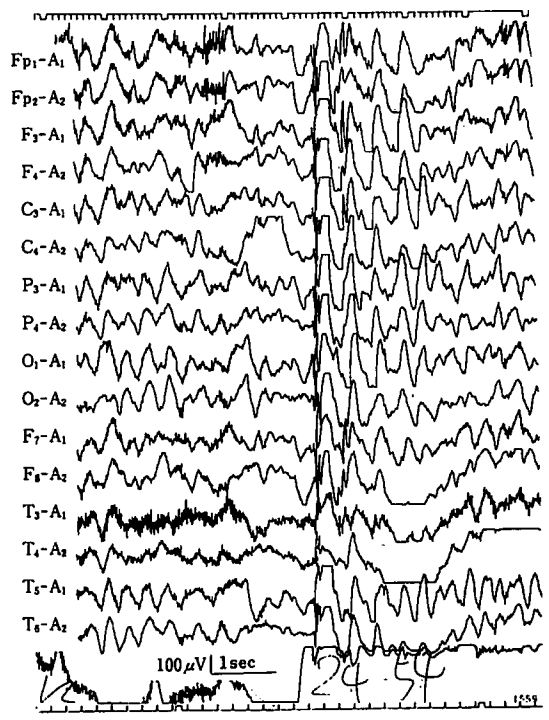

Fig. 2: Three-year-old girl; myoclonic seizure.

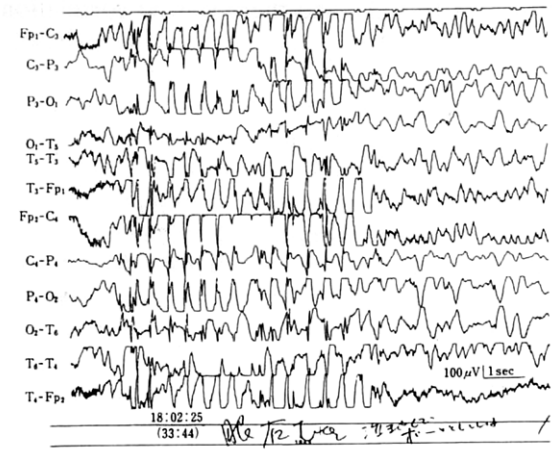

Fig. 3: One-year-old boy; atypical absence.

the other hand, 10 patients had CPS only temporarily, continuing to have it for 2 months to 6 years. In eight of these 10 patients, CPS disappeared before the age of 6 years. In those who still had CPS after the age of 6 years, the seizures became to occur primarily during sleep after the age of 7 years. Ictal EEGs were recorded 25 times in eight patients (Fig. 4). CPS evolved into generalized tonic–clonic convulsions in six records in three of these patients (Fig. 5). The seizure originated in the frontal region in six records, temporal region in nine records, and occipital region in six records. In four records, the seizure origin could not be determined. In three patients, the seizure origin of the seizure varied from one seizure to the other even in the same patient.

All 14 patients had GMS. GMS was noted consistently throughout the follow-up period in

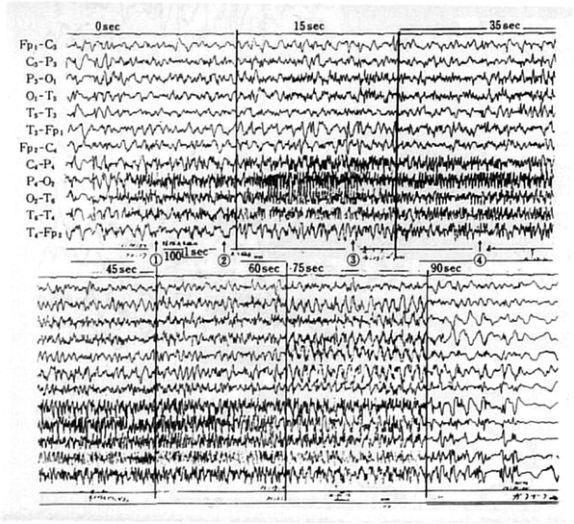

Fig. 4: Two-year-old girl; complex partial seizure.

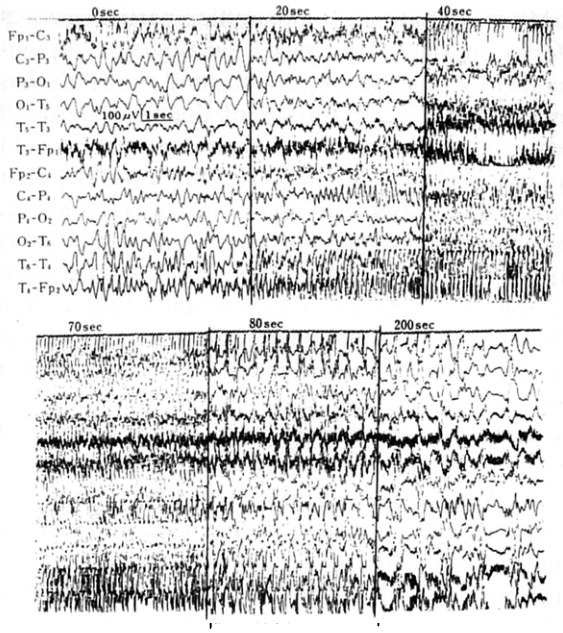

Fig. 5. Three-year-old girl; secondarily generalized seizure.

11 (79%), but unilateral dominant seizures became less frequent after the age of 7. In three patients, GMS disappeared temporarily for 10 months to several years in three. In two of these three patients, other types of seizure also disappeared simultaneously. In the remaining one patient, AA and MS persisted even after the disappearance of tonic–clonic convulsion. Similarly to CPS, GMS occurred primarily when the patients were awake in infancy, but episodes during sleep increased from the age of 6–7 years and become dominant after the age of 9–10 years. Unilateral dominant tonic–clnonic convulsion in 11 patients, but the side of dominance was inconsistent, and both right-side dominant and left-side dominant convulsions were noted in the same patients. Ictal EEGs were recorded 17 times in seven patients (Fig. 6). GMS was preceded by MS in two of these episodes in two patients (Fig. 7).

Four patients showed photosensitivity (three of them have been reported previously[2,3]). Self-

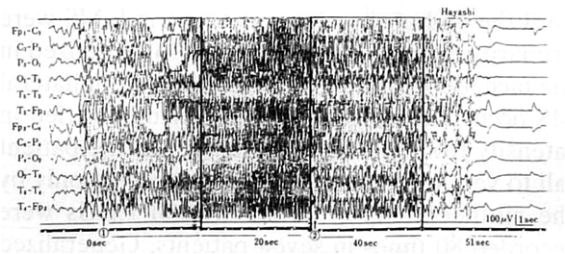

Fig. 6: One-year-old boy; tonic–clonic seizure.

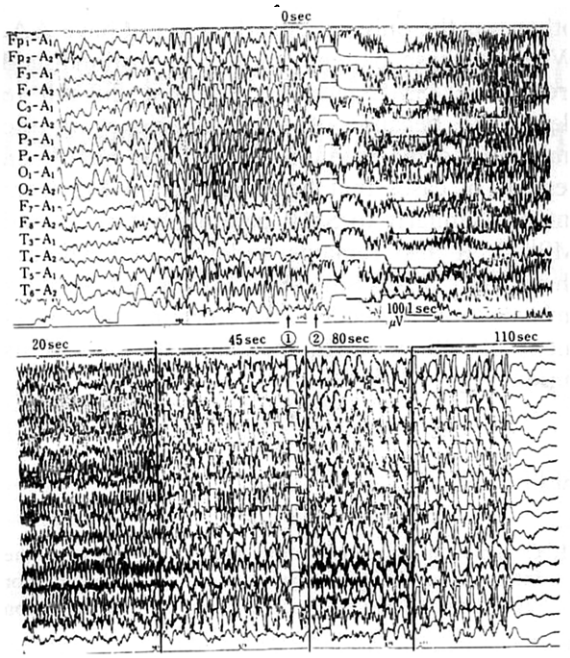

Fig. 7: Three-year-old boy; myoclonic tonic–clonic seizure.

induced seizures were noted in two of them[3]. Photosensitive seizures consisted of MS in three patients and GMS in one, and occurred between the age of 11 months and 5 years (mean 2 years 8 months). In one patient (case 5), photo-induced MS disappeared after age 1 but recurred at age 7. In another patient (case 6), MS induced by sunlight disappeared, but photoconvulsive responses on EEG persisted. In the next patient (case 11), GMS was induced by stroboscope during EEG recording at the age of 3 years, but no photosensitivity was noted in daily life. In the last patient, MS were repeatedly induced by the sunlight but not by stroboscope during EEG.

At the onset of epilepsy, EEGS showed no epileptiform discharge in any of the patients. Epileptic discharge began to appear on the EEG from the age of 11 months to 8 years (mean 2 years and 10 months). The epileptiform discharge noted for the first seizure was generalized or unilateral dominant generalized spike and wave complex in all patients. In addition, multifocal spikes or sharp waves were noted in five patients. The appearance of epileptic discharge was unstable, and it often disappeared temporarily, but no correlation was observed between the appearance and disappearance of epileptic discharge and the frequency of seizures. The background activity was normal at the onset of epilepsy but became to consist of theta waves dominant in the centro-parietal region at the age of 1–3 years (mean 2 years 4 months). The theta wave activity continued to appear on EEG until the end of follow-up in all patients.

During follow-up, four to 11 (mean six) antiepileptic drugs (AEDs), but not more than five at the same time, were given per patient throughout the follow-up period. None of the drugs completely suppressed any type of seizures. The frequency of seizures tended to decrease with age in all patients, but this was unlikely to be due to the AEDs, in the two patients in whom GMS and CPS disappeared temporarily. For example, when the seizures disappeared, no new AEDs were added and blood concentration of AED prescribed remained stable. Valproate and clonazepam slightly reduced the frequency of MS and AA in some patients but did not completely eliminate seizures, at least in the short-term spans. Diazepam and phenobarbital showed some effects on prolonged or clustering GMS or CPS. In addition, phenytoin, carbamazepine, primidone, ethosuximide, zonisamide, acetazolamide, acetylphenetunide, allopurinol, nitrazepam, clobazam, and sultiam were administered.

DISCUSSION

The SME patients in this study showed similar clinical features and clinical course with the exception of seizure symptoms. They had no perinatal abnormalities and presented with no findings suggestive of organic brain lesions by neuroimaging studies. They showed normal motor development prior to onset of epilepsy, but exhibited gradual retardation in the psychomotor development from the age of 1–2 years. They all became able to walk without assistance, but the gait was often unstable. Some patients learned meaningful words but all patients remained unable to communicate. After the age of 3, however, none of them revealed marked psychomotor regression. The background activity on EEG became to consist of centro-parietal dominant theta waves after 1 year of age, and this characteristic activities continued to appear up to the end of follow-up. In contrast to these similarities in clinical features, seizure symptoms varied considerably among the patients. There was no common tendency in the order of their appearance and duration of the persistence. One exception was GMS, which was the initial seizure type and continued to occur to the end of the observation period in most patients. As suggested by other investigators, GMS is the most consistent core seizure type in SME. As for the causes of this variability in the pattern of the appearance

of seizures, the effects of AEDs may be considered first. However, the present study showed that none of the drugs completely suppressed any seizure type at least in a short time span. Moreover, there were no changes in the dose or the blood concentration of AEDs before or after the disappearance of seizures in not a few patients, including the two patients who experienced temporary disappearance of tonic–clonic and CPS. Therefore, the differences in the seizure pattern among the patients cannot be ascribed simply to the effects of AEDs. Another possible explanation of the differences in the pattern of appearance of seizures may be that SME is an epileptic syndrome caused by multiple aetiology. West syndrome develops on the basis of diverse impairments of the central nervous system and exhibits widely different clinical courses. However, SME shows considerable commonness in neurological symptoms other than seizure symptoms, and this suggests a single aetiologic mechanism. Fujiwara *et al*[4] reported that the clinical course of neurological symptoms, was similar including seizure symptoms, between identical twins. We noted the same tendency in the twins in the present study, and this also supports the possibility that SME is a clinical entity due to a single aetiologic mechanism rather than an epileptic syndrome due to multiple causes. The variability in the evolution of seizures may be explained by differences in the epileptic threshold among patients. The similarity in the seizure profile between twins may be a result of the similarity in the epileptic threshold.

SME is an epileptic syndrome first described by Dravet *et al*[5] Their early report showed CPS in only five (12%) of the 42 patients[6]. In a recent report by the same authors[7], however, the frequency of CPS in SME was 46%. On the other hand, Ohtsuka *et al*[8] reported as high frequency of CPS as 13 (93%) of 14 patients, similar to our results. The discrepancy in the frequency of CPS among investigators may be partly explained by the difference in the follow-up period. Rossi *et al* reported that the frequency of partial seizure, which was only 33% within 1 year after the onset, increased to 60% 8–23 years after the onset[9]. The former literature reported the age of the onset of MS was 1–4 years in SME. However, we did not set the upper limit in the age of the onset of MS for our criteria of SME, and there were two patients who began to have MS at the age of 5 years. In one of these two patients, all seizures disappeared during the observation period. The other was the only patient who did not have AA. Whether these patients should be distinguished from other SME patients or not is difficult to determine because of the insufficiency in the number of subjects in this study. There have been reports of cases that had refractory GMS from infancy similarly to SME patients but never had MS[10,11]. It also remains undetermined whether these cases be classified as SME or not. Further investigation is needed to determine the placement of MS in SME, including the age of its onset.

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