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Spinal muscular atrophy and progressive myoclonic epilepsy: one case report and characteristics of the epileptic syndrome

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Review

Summary *Introduction*: Spinal muscular atrophies (SMAs) are a group of degenerative diseases primarily affecting the anterior horn cells of the spinal cord and motor cells of cranial nerve nuclei. Even if the clinical picture is mainly dominated by the diffuse muscular atrophy, in some cases, patients may show associated, atypical clinical features (''SMA plus''). In particular, the association of SMA and progressive myoclonic epilepsy (PME) has been rarely described. *Case report*: We present the clinical and electrophysiological data of a boy with childhood-onset SMA associated with PME and reviewed cases of the literature. *Conclusion*: The association of SMA with PME may constitute a separate and, probably, genetically independent syndrome with unique clinical and electroencephalographic findings or, at least, a variant of a neurodegenerative or metabolic disease, due to yet unknown causes.

Introduction

Spinal muscular atrophies (SMAs) are a group of relatively common diseases, usually occurring in infancy or early childhood, transmitted by autosomal recessive inheritance and characterized by loss of motor function and muscle atrophy due to degeneration of the anterior horn cells.[1,2] Depending on the age of onset and the survival of patients, different forms of SMAs have been recognized.[1–3] Even if the clinical picture is mainly dominated by the diffuse muscular atrophy, some patients can also show atypical clinical features (e.g. oculomotor palsy, epilepsy, nerve deafness, olivopontocerebellar atrophy, multiple arthrogryposis, etc.).[1–3] In the last few years, experts particularly focused attention on the so-called ''SMA plus'' phenotypes and suggested clinical and genetic heterogeneity.[3] Here, we present the clinical and electrophysiological data of a boy with childhood-onset SMA associated with progressive myoclonic epilepsy (PME) and review data from the literature. In particular, we focus on the features of the epileptic syndrome.

Case report

This 12 years old, right-handed boy was the first child of two brothers, born at term after an uneventful pregnancy to nonconsanguineous parents. His younger brother was in healthy condition. Familial history was negative for neuromuscular disorders or epilepsy. The patient was completely

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asymptomatic and age appropriate in all his activities until the age of 4 years. Then, he developed progressive weakness and became slow and clumsy. The parents noticed gait disturbance, difficulty in running and getting up from the floor. In addition, the patient developed progressive nerve deafness, dysarthria and dysphagia. At the age of 9 years, the boy experienced daily, brief episodes of loss of consciousness, usually accompanied by myoclonic jerks of the upper limbs and, sometimes, with head nodding; in addition, the patient also presented atonic seizures in which he fell to the floor, with preserved consciousness. He came to our observation at the age of 12 years. Neurological examination showed diffuse muscle atrophy, involving both upper and lower extremities with associated shoulder girdle atrophy and pseudohypertrophy of the calves. There was mild facial weakness and deficiency in oromotor function. Conspicuous fasciculations of the tongue and postural hand tremor were also observable. In order to obtain seizure control, valproate (500 mg b.i.d.) and clobazam (2.5 mg t.i.d.) were started. Episodes reduced in frequency and intensity; however, complete seizure control was never achieved. During the following months, the clinical course drastically worsened and respiratory infections became more severe. The patient died from inhalation pneumonia at the age of 14. Parents did not give permission for autopsy.

Investigations

Brain MRI was normal. Neuropsychological study revealed an average intelligence with no impairment of cognitive functions. Electroencephalography (EEG) showed diffuse slowing in the theta range of background activity with frequent, irregular, generalized spike-and-wave (SW) and polyspike-and-wave (PSW) complexes at 2—2.5 cycles/s (Fig. 1). Paroxysmal activity was increased by intermittent photic stimulation and by hyperventilation. During the recording, the boy presented several episodes of brief absences (2—4 s) with associated myoclonia at the eyelids and at upper limbs or brief head

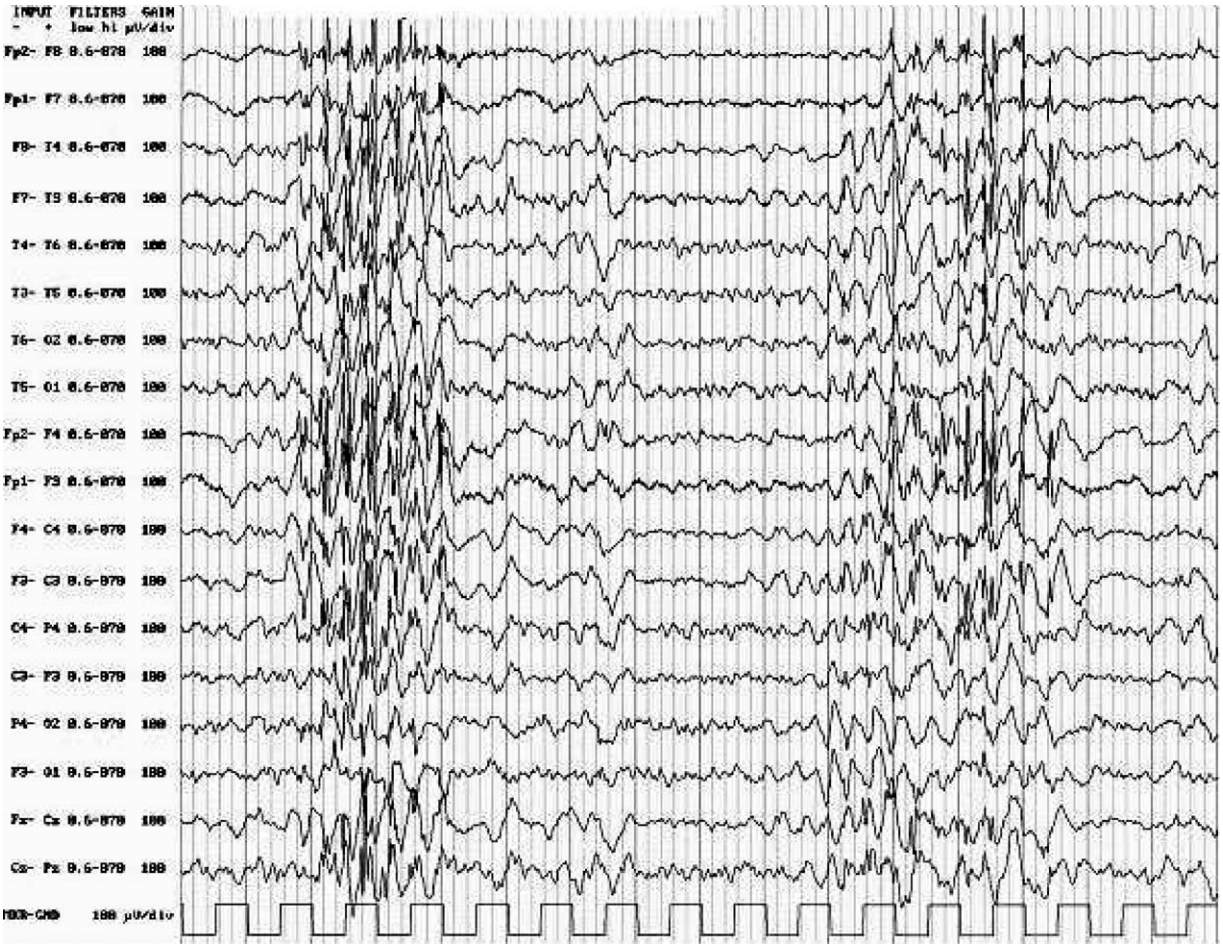

Figure 1 Electroencephalography (EEG) shows diffuse slowing of background activity, in the theta range, and two brief bursts of generalized spike- and polyspike-and-wave complexes at 2—2.5 cycles/s.

nodding, synchronous with bilateral SW and PSW. Paroxysmal activity was not significantly modified during sleep. In addition, the boy had a fine tremor at the hands, more evident maintaining a posture and apparently not related to the paroxysmal activity. Surface electromyography (EMG) showed irregular, arrhythmic, high-frequency activity without any regular alternation between agonist and antagonist muscles, as found in tremor, and sporadic myoclonic jerks (Fig. 2). Jerk-locked back-averaging (JLA) did not demonstrate any cortical event time-related to myoclonus. Somatosensory evoked potentials and long latency reflex I were within the normal range. Brainstem auditory evoked potentials were consistent with dysfunction of either central and peripheral pathway and audiometry revealed sensorineural deafness. In all muscles examined, EMG disclosed fasciculations, impaired recruitment with increased firing rate of the motor units and polyphasic, high-amplitude, long duration potentials. Motor and sensory conduction velocities were within the normal values. These features identified lower motor neuron degeneration. Hematoxylin—eosin stained muscle biopsy of right quadriceps revealed a typical denervation pattern with large groups of small, atrophic Type II fibers adjacent to groups of hypertrophied ones, with abundant perimysial adipose and connective proliferation. Myofibrillar ATPase reaction revealed that the atrophic fibers were of Type II whereas the normal and hypertrophied ones were of Type I. After Trichrome staining, no red ragged fibers were observed. DNA analysis failed to demonstrate deletions or point mutations in the motor neuron (SMN) gene.

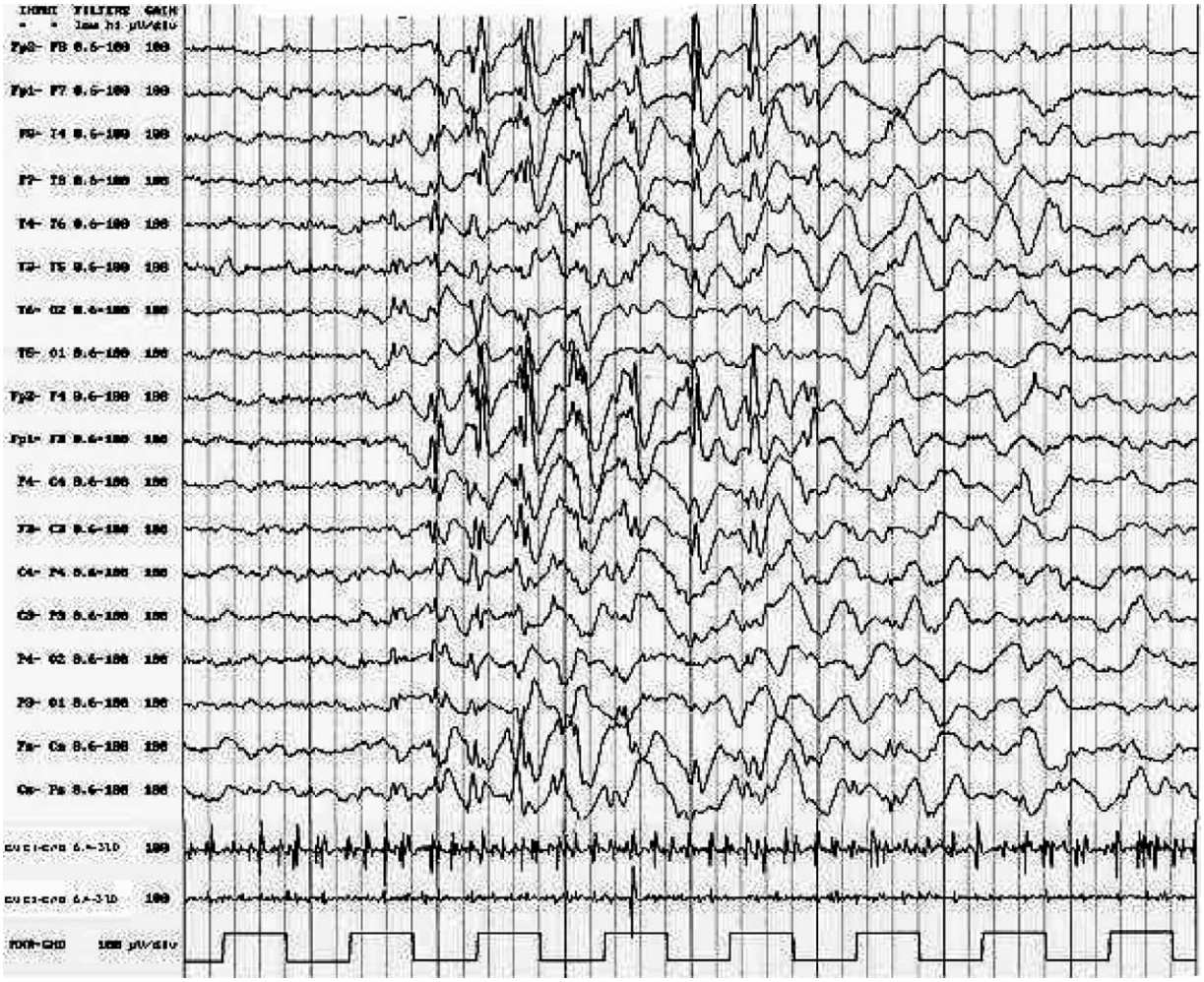

Figure 2 Polygraphic-EEG during postural maintenance of both arms against gravity. Brief electroclinical seizure (absence accompanied by eyelid and upper limbs myoclonia). EEG recording shows bilateral, predominantly anterior, generalized spike- and polyspike-and-wave complexes at 2—2.5 cycles/s. Surface-recorded electromyography (EMG) shows synchronous and asynchronous jerks prevalent on the right wrist extensor not correlated with the EEG paroxysmal activity. In addition, sporadic, isolated myoclonic jerks are also observed (EMG1: right wrist extensor; EMG2: right wrist flexor).

Discussion

SMAs are a group of degenerative diseases primarily affecting the anterior horn cells of the spinal cord and motor cells of cranial nerve nuclei.[1,2] Carrier frequency has been estimated to fall between 1 in 50–80 and the overall incidence of the disease is of 1 in 10,000–25,000. Different types of SMA have been recognized depending on the age of onset and on the length of survival: SMA I (Werdnig–Hoffman disease), with onset from the prenatal period through the first months of life, SMA II (intermediate form), with onset ranging between 2 and 6 months, SMA III (Wohlfart–Kugelberg–Welander disease), manifesting after the age of 12 months, and adult-onset SMA IV.[1,2] However, overlap is present in some families, and all these conditions are linked to the same chromosomal region, 5q11.2-q13.3. Thus, they are considered allelic disorders with an earlier onset related to more frequent deletions in SMN gene.[1–5] Clinical suspicion of SMA is confirmed by laboratory, EMG and muscle biopsy.[1,2] Creatinine kinase can be sometimes slightly elevated but not by much. Electrophysiological studies and muscle biopsy are of paramount importance since they allow confirming of motor neuron disease. Nowadays, genetic analysis allows definitive diagnosis: most patients shows deletion of exons 7 and 8 of the SMN gene;[6,7] microdeletions or point mutations can sometimes be detected.[4] Genetically different SMA variants, showing additional, atypical clinical features, have been also described and proved to be not linked to 5q.[3] In particular, an intriguing clinical picture characterized by the co-existence of SMA and PME has been described rarely in the literature.[8–15] Jancovic and Rivera first described a North American pedigree in which three members showed slight mental retardation, adult-onset myoclonic epilepsy, in association with predominantly distal signs of SMA which followed a quite benign course.[9] Lance and Evans reported autopsy findings of a Finnish boy, who developed action myoclonus, generalized seizures and muscular atrophy during childhood. Bilateral sensorineural hearing loss was also present. Autopsy revealed the degeneration of cranial nerves' motor neurons and spinal anterior horn cells, with neuroaxonal dystrophy of gracilis and cuneatus nuclei; no alterations were observed in the cortex, thalamus, basal ganglia and cerebellum.[10] D'Ecclesia et al.[11] and Taglioli et al. [12] independently reported two pairs of Italian brothers showing the combination of juvenile-onset amyotrophic syndrome, action myoclonus and generalized seizures, without nerve deafness. In a late stage of the disease, the patients developed bulbar symptoms, such as dysphagia and dysarthria. However, in Jancovic and Rivera's family, patients had a more precocious onset of symptoms, a predominantly proximal distribution of muscular atrophy and a more severe clinical course. The two brothers described by Marjanovic et al. showed proximal signs of SMA, action myoclonus and drug-resistant generalized epilepsy but not deafness.[13] More recently, Higashi et al.[14] reported a 37-year-old women with genetically proved SMA, associated with temporal lobe epilepsy and MRI finding of hippocampal sclerosis. Finally, Haliloglu et al.[15] reported four patients from two families, showing a similar clinical picture to the two brothers of Marjanovic et al. [13] and without evidence of SMN1 gene mutations. Our patient presented a childhood-onset SMA with associated PME and deafness as in the aforementioned cases. Thus, from review of the literature data, we suggest that the association of SMA with PME may constitute a separate syndrome with a homogeneous clinical and EEG picture, not linked to chromosome 5. Mode of inheritance suggests a recessive disorder. Epilepsy usually appears in the late infancy, later than the SMA onset, and it is mainly characterized by severe, drug-resistant, generalized epilepsy. A detailed analysis of the epileptic syndrome has not been provided for the previous reports. The fine, postural twitching of the hands, that can be considered, on the basis of EMG, a myoclonic activity rather than a true tremor, it is not correlated with the EEG paroxysmal activity; furthermore, JLA failed to demonstrate its cortical origin. Based on this findings, this tremor could be considered similar to minipolymyoclonus, as reported by Spyro in the setting of juvenile motor neuron disease.[16,17] Our patient, as in other similar cases, developed sensorineural deafness. In summary, this condition seems to delineate a peculiar form of ''SMA plus''. This concept has been recently developed since various SMA phenotypes with additional clinical features have been described: a predominantly distal form of SMA with severe respiratory distress (SMARD) has been mapped to chromosome 11q;[18] a pedigree with SMA associated with arthrogryposis and congenital fractures was linked to Xp11.3-q11.2;[19] and a form with pontocerebellar hypoplasia has been demonstrated to be not linked to 5q.[20] In our case, epilepsy was probably not the most important component of the disease. According to the concept of PMEs, a heterogeneous group of progressive diseases, SMA plus might be considered as a rare form of PME. However, in contrast with the other PMEs, in which epilepsy and myoclonus are the presenting symptoms, in this form, epilepsy as well as deafness appeared later during the evolution of the disease. The collection of similar cases

is needed to better define distinct phenotypes, in order to perform genetic studies as well as to identify new genes and molecular pathogenetic mechanisms involved in this condition.

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