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Case Report

Progressive myoclonic epilepsy type 1: Report of an Emirati family and literature review

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ABSTRACT

Purpose: Progressive myoclonic epilepsy type one is a neurodegenerative disorder characterized by action- and stimulus-sensitive myoclonus, tonic–clonic seizures, progressive cerebellar ataxia, preserved cognition, and poor outcome. The authors report clinical, neurophysiological, radiological, and genetic findings of an Emirati family with five affected siblings and review the literature.
Methods: All data concerning familial and clinical history, neurologic examination, laboratory tests, electroencephalogram, brain imaging, and DNA analysis were examined.
Results: Genetic testing confirmed the diagnosis of autosomal recessive progressive myoclonic epilepsy type 1 (EPM1) in two males and three females. The median age at onset was three years. Action- or stimulus-sensitive myoclonus and generalized seizures were recorded in 100% of our patients, at median age at onset of 3 and 4 years, respectively. Multisegmental myoclonus and generalized status myoclonicus were observed in 80% of our patients. Dysarthria and ataxia developed in 100% of our patients. Vitamin D deficiency and recurrent viral infections were noticed in 100% of our cohort. Cognitive, learning, and motor dysfunctions were involved in 100% of our patients. The sphincters were affected in 60% of our patients. Abnormal EEG was recorded in 100% of our cohort. Generalized brain atrophy progressively occurred in 60% of our patients. Phenytoin and carbamazepine were used in 60% of our patients with worsening effect. Valproate and levetiracetam were used in 100% of our patients with improving effect.
Conclusions: This is the first to report a family with EPM1 in UAE. Our study emphasized a particular phenotype expressed as earlier disease onset, severe myoclonus, and generalized seizures. Cognitive, cerebellar, motor, and autonomic dysfunctions and brain atrophy were also earlier at onset and more severe than previously reported. Recurrent viral infections are another unique feature. This constellation in tout à fait was not previously reported in the literature.

1. Introduction

Progressive myoclonic epilepsy type 1 (EPM1) or Unverricht–Lundborg disease (ULD) is an autosomal recessive disorder [1]. It is considered the most common and less severe form of progressive myoclonic epileptic syndromes. It was initially recognized in Finland, where prevalence and incidence are 5 and 4 in 100 000 births, respectively [2]. Clusters of phenotypically and, sometimes, genetically identical disorders occur in southern Europe and North Africa [3]. Its prevalence has recently increased in the Mediterranean region [4]. However, recent studies suggested that it may be underdiagnosed in many countries [5]. Regions of higher prevalence are found in places with common founder effect or high rates of consanguineous marriages.

Progressive myoclonic epilepsy type 1 starts in children at 6–16 years of age. Its onset is characterized by myoclonic jerks and/or tonic–clonic seizures. Generalized tonic–clonic seizures are the presenting feature in many cases [6]. Action- or stimulus-sensitive myoclonus is an essential feature for diagnosis and the first symptom in half of the patients [7]. It is usually fragmentary and multifocal and is often triggered by variable stimuli. It is particularly apparent in muscles of the face and distal limbs. Bilateral massive myoclonus tends to involve proximal limb muscles closest to the torso [6]. This disabling myoclonus promotes risk

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of injury and impairment of daily living activities. Neurological examination is normal initially, however, intention tremor, dysarthria, and ataxia develop later. Mild dementia is typically a late feature. Intellectual deficit develops very late [8].

Electroencephalograph (EEG) demonstrates spontaneous spike and polyspike–wave complexes, photosensitivity, and background slowing [1]. Initially, brain MRI is usually normal. It is often mistaken for the more common juvenile myoclonic epilepsy (JME). However, it is not currently possible to diagnose EPM1 without a genetic test. Earlier onset cases often resulted in premature need of wheelchair or death before their midtwenties [9]. Modern antiepileptic therapy has gradually increased life expectancy [6]. Phenotypes result from the interaction of genes and environment. Therefore, it is crucial to determine presenting phenotypes, its variability, influencing factors, and phenotype–genotype association. We describe clinical, electrophysiological, and radiological aspects, in addition to genetics and management of an Emirati family, and review relevant literature.

2. Patients and methods

Index patients in our family are the second and third, both seen in May 2004. They belong to an Arabian family consisting of parents and eleven siblings. Both reported an older sibling more severely affected, bedbound, and mentally retarded. Both suffered early morning myoclonic jerks, stimulus- and action-sensitive myoclonus, and generalized seizures. All three were the product of a normal pregnancy and uneventful full-term vaginal delivery. Their parents are first-degree cousins. Differential diagnosis included PME, JME, idiopathic myoclonic epilepsy, and subacute sclerosing panencephalitis. Therefore, the index patients were extensively investigated. Hematologic, metabolic, mineral, endocrine, and vitamin profiles were arranged. Ancillary studies like C-reactive protein, ferritin, homocysteine, methylmalonic acid, alpha-fetoprotein, hemoglobin electrophoresis, drug levels, ECG, echocardiogram, and Holter monitoring were done as indicated. Quantitative amino acid testing in urine of 28 amino acids; enzymatic assay of alpha- and beta-galactosidases in leucocytes, GM1 gangliosidosis, and very long-chain fatty acids including phytanate and pristanate levels; skin and muscle biopsy with special histochemistry; and mitochondrial DNA (mtDNA) analysis were done in the first and third patients to rule out MERRF. Brain Electroencephalograph, brain CT, and MRI brain and measles antigen–IgG in the blood and in CSF were needed. Genetic DNA testing was done first in these two patients using PCR analysis and Southern blotting. When these returned as positive for the *CSTB* gene, the other three affected siblings and parents were tested. The genetic pedigree is shown in Fig. 1. Demographic and clinical data were tabulated (Tables 1 and 2), further analyzed, and compared with contemporary literature.

3. Results

Genetic testing confirmed the diagnosis of autosomal recessive EPM1 in five, two males and three females, who constituted our probands. It was done by taking blood samples from each patient and performing molecular testing by PCR fragment analysis and genomic Southern blotting. Polymerase chain reaction (PCR) failed to detect normal *CSTB* alleles, whereas Southern blotting revealed expanded alleles with more than 30 dodecamers. Both expanded alleles were estimated to contain a maximum of 100–120 repeats in the first three patients and a minimum of 80 repeats in the remaining two patients; the highest repeat was recorded in our first patient. Results confirmed the diagnosis of autosomal recessive EPM1 in all our probands (100%). Genetic testing was done for both parents, PCR detected normal *CSTB* signal, whereas Southern blotting revealed normal and expanded allele with 100 dodecamer repeats. The sequences of *CSTB* exons including adjacent splice signals correspond to those of published references [10]. Results confirmed the EPM1 carrier status of one expanded *CSTB* allele repeat in each parent. The median age at onset of disease was three (range: 2–4) years (Table 1). Early morning myoclonic jerks and action- or stimulus-sensitive myoclonus and generalized tonic–clonic seizures were recorded in 100% of our patients. The median age at onset of myoclonus and generalized seizures was also earlier at 3 and 4 years, respectively. Multisegmental myoclonus and generalized status myoclonicus occurred in 80% of our patients. Dysarthria and ataxia were observed in 100% of our patients at a mean age of 8 years. Frequent and recurrent traumas and notably viral infections were noted in 100% of our patients (Table 2). Severe sphincter dysfunction was reported at a median age of 6 years in 60% of our patients. Cognitive dysfunction complicated the clinical picture in 100% of our patients at a mean age at onset of 8 years. Difficulty in learning was detected in 100% of our patients, with 60% of them having moderately severe learning difficulty. Spasticity and motor dysfunction were steadily progressive and involved 100% of our patients at a median age of 7–8 years. Vitamin D deficiency was observed in 100% of our cohort. Electrocardiogram ECG was abnormal in one patient and showed short PR interval, nodal rhythm, mild bradycardia, and paroxysmal atrial fibrillation. EEG was abnormal in 100% of our cohort. Brain CT and MRI were initially normal in 80% of our patients. Central and peripheral brain atrophy gradually progressed in 60% of our patients. The second patient had initially isolated vermian atrophy. Muscle biopsy to detect striated ragged red fibers and enzymatic changes in respiratory chain to rule out mitochondrial encephalopathy with striated ragged red fibers (MERRF), skin biopsy to detect Lafora bodies, and mitochondrial DNA analysis were done in one patient each, and all were negative. Phenytoin and carbamazepine were initially used for only 2–4 months in 60% of our patients with worsening effect. Valproate, clonazepam, and levetiracetam were used in 60% of our patients with seizure improvement. Valproate and levetiracetam were the sole agents used in 40% of our patients.

Table 1
Demographics and clinical features.

Age	Sex	Onset	EMJ/SSM	Multis M	Stat Myoc	GTC Seiz	Dysarthria	Ataxia
31 y	M	2 y	2 y	+	+	3 y	Severe	Severe
30 y	M	3 y	3 y	+	+	4 y	Severe	Severe
18 y	F	3 y	3 y	+	+	4 y	Severe	Severe
14 y	F	3 y	3 y	+	+	4 y	Mild	Mild
12 y	F	4 y	4 y	−	−	5 y	Mild	Mild

EMJ: early morning jerks, SSM: stimulus-sensitive myoclonus, Multis M: multisegmental myoclonus, Stat Myoc: status myoclonicus, GTC Seiz: generalized tonic–clonic seizures, y: year, M: male, +: positive, F: female, −: negative.

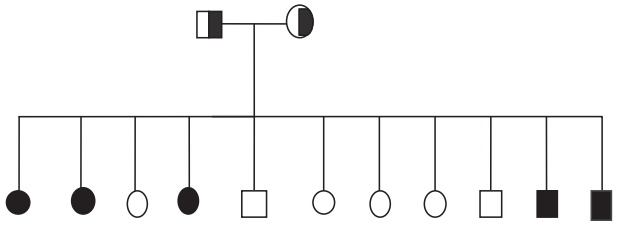

Fig. 1. Genetic pedigree shows the carrier status of parents and the affected two brothers and three sisters.

4. Discussion

This family consisted of parents who are carriers of the *CSTB* gene and five siblings confirmed to have EPM1, two males and three females. The median age at onset of the disease was 3 (range: 2–4) years (Table 1) versus 6–15 years in the published literature [2,11]. This is an entirely new finding which was not previously reported in this common disease mutation in the literature. Early morning myoclonic jerks and action- or stimulus-sensitive myoclonus were recorded in all our patients (100%). Myoclonus was the first symptom in 100%, and the median age at its onset was 3 years in our cohort.

Table 2
Demographics and complications.

Pat	Trauma	Infection	Cognition	Learning D	Spasticity	M Dysfun	Sphincters
31 y M	+	+	MR 3 y	Severe	Severe 5 y	Bbound 5 y	3 y
30 y M	+	+	IQ 76, LSc 8 y	Moderate	Moderate 7 y	Wchair 8 y	7 y
18 y F	+	+	IQ 76, LScD 9 y	Moderate	Moderate 7 y	Wchair 8 y	8 y
14 y F	+	+	IQ 81, 10 y	Mild	Mild 8 y	Mild 9 y	−
12 y F	+	+	IQ 82, 10 y	Mild	Mild 8 y	Mild 10 y	−

Pat: patient, D: difficulty, M Dysfun: motor dysfunction, Y: year, M: male, +: positive, MR: mental retardation, Bbound: bedbound, IQ: Intelligence Quotient, LSc: left school, Wchair: wheelchair, F: female, LScD: left school of disabled, −: negative.

However, myoclonic jerks were the first symptom in just a little over 50% of cases, and the median age at onset was 12.1 years in published literature [6,9]. Multisegmental, asynchronous myoclonus and status myoclonicus occurred in 80% of our patients (Table 1). Typically, action- or stimulus-sensitive myoclonus is an essential feature for diagnosis. Generalized tonic–clonic seizures were observed in 100% of our cohort at a mean age of 4 (range: 3–5) years. However, they were observed in almost 50% of cases at a mean age of 10.8 years in the relevant literature [6,11]. Symptoms inexorably progressed in one-third of reported patients in their midtwenties [2,6], while 60% of our family became bedbound or wheelchair-bound at a mean age of 7 years.

Neurologic examination is initially normal. However, an experienced neurologist clinically pinpoints recurrent, almost cryptic myoclonus in response to various stimuli and actions including photic stimuli, threats, clapping of hands, and loud noises produced during the examination. This was observed early in our patients (2–4 years). Dysarthria and ataxia were observed in 100% of our patients, with 60% of them having a severe form of dysarthria and ataxia compared with almost 50% of patients in literature [6,11] (Table 1).

Frequent and recurrent trauma was one of the most common complications observed in !00% of our cohort and led to various fractures, joint twists, and strains. An interesting feature which was sparingly reported is frequent and recurrent notably viral infections in 100% of our cohort (Table 2). Moderate to severe sphincter dysfunction was featured in 60% of our patients at a median age of 6 years. Cognitive dysfunction complicated the clinical picture in 100% of our patients at a mean age of 8 years, it was particularly severe in the first patient who was mentally retarded in early childhood and did not attend school with healthy peers. The second and third patients have moderate and progressive learning difficulty and left their regular and disabled schools at 8–9 years. The IQ of both was considered borderline impaired (IQ: 76). Learning difficulty was prominent in 60% of our patients. The fourth and fifth patients have early learning difficulty at 10 years of age with IQs of 81–82 on Wechsler's intelligence scale which rank them below low moderate status. Mental retardation is an unusual finding in EPM1 [8]. Cognitive dysfunction and progressive learning difficulty were defined as rare and late features. Dementia and intellectual deficit, if present at all, have been reported to develop very late [2,8]. Spasticity and motor dysfunction were moderate to severe in 60% of our patients and observed at median age of 6–7 years (Table 2). Learning and motor dysfunctions were both steadily progressive and may have a certain degree of synchronization. This is entirely different from the published literature, as mild dementia and ataxia are typically late features [6,8]. Curiously 100% of our cohort showed vitamin D deficiency. The exact relation to this phenotype is presently unknown. Phenotypic expression is variable, even in the same region, however, this constellation of unusual multiple clinical features in our family may impose a special and independent phenotype.

Disease course in our cohort seems inevitably progressive. The phenotype is more heterogeneous than previously assumed. It was noticed previously that only few patients become wheelchair-bound, and significant interpersonal fluctuations will be observed for many years before losing the ability to walk. In contrary, 60% of our patients lost their ability to walk within 5–8 years. Variable intensity of symptoms and speed of disease progression can also vary even within the same family. It was suggested that patients from Finland and North African regions share a common ancient founder effect [12]. Prevalent use of phenytoin in Finnish patients was claimed to be a major factor in clinical differences between both regions. In our cohort, phenytoin was used in our first three patients for only 2–4 months, and this period cannot be assumed responsible for changes in our phenotype. Environmental factors and differences in diet composition stand out as the logic explanation for differences in disease course not only between different regions but also within the same region or even the same family. However, this speculative effect on disease phenotype remains to be proven [13,14]. Progressive myoclonic epilepsy type 1-like phenotype with earlier onset, linked to chromosome 12, was described in an inbred Arab family [15], and the causative gene remained unknown. It was also reported in a North Sea phenotype that the causative gene was GOSR2 [16]. However, our phenotype was positive for classical *CSTB* mutation.

Laboratory tests were not helpful; however, in working through the differential diagnosis, biochemical and enzymatic assays become useful in excluding important masquerades. This was true with our first three patients. ECG in the second patient showed short PR interval, nodal rhythm, mild bradycardia, and paroxysmal atrial fibrillation. The exact relationship to EPM1 is not presently known.

Diagnosis should be expected in normally developing 6- to 16-year-old children who present with action myoclonus, tonic–clonic seizures, marked photosensitivity, gradual worsening of stability, and normal cognition [17]. However, such a statement is no longer completely accurate as our family had earlier disease onset and more rapid deterioration. Differential diagnosis is crucial; if action myoclonus is absent, patients can be easily misdiagnosed with JME [18]. In exceptionally severe progression of cognitive or visual symptoms, Lafora's disease, myoclonic epilepsy with ragged red fibers (MERRF), neuronal ceroid lipofuscinoses (NCL), and sialidoses should be considered [2].

EEG was abnormal in 100% of our cohort; it showed generalized polyspike, spike, and slow-wave (GPSSW) complexes in 60% (Fig. 2), generalized paroxysmal polyspikes and slow waves (GPPSW) in 20% (Fig. 3), and generalized low amplitude spike and slow wave (GSSW) complexes in 20% of our patients. The background was normal during early years of the course. Photosensitivity was prominent. Focal epileptiform changes, in either occipital region, were observed in 40% of our cohort and reported elsewhere in 25% of patients [11,17].

Therefore, focal changes coexisting with generalized findings cannot exclude EPM1. In addition, physiological sleep patterns disappeared in 60% after 8 years in our cohort compared with those in 50% in the literature after 16 years of disease [17]. This is different from Lafora's disease in which disappearance of physiological sleep pattern is an early recognized and constantly progressing feature [6]. The majority of myoclonic jerks are not time-locked to EEG discharges. This can lead to the wrong conclusion of psychogenic seizures [19]. It would be important to study the EEG features of the current phenotypes at different stages of the disease.

Brain CT and MRI were completely normal in 40% of our patients. This is usually observed at the time of diagnosis, while, at later stages, atrophy of the medulla, cerebellum, pons, midbrain, and, less often, cerebral hemispheres was observed [4,20]. Mild central and peripheral atrophy was observed earlier in 60% of our cohort. However, one

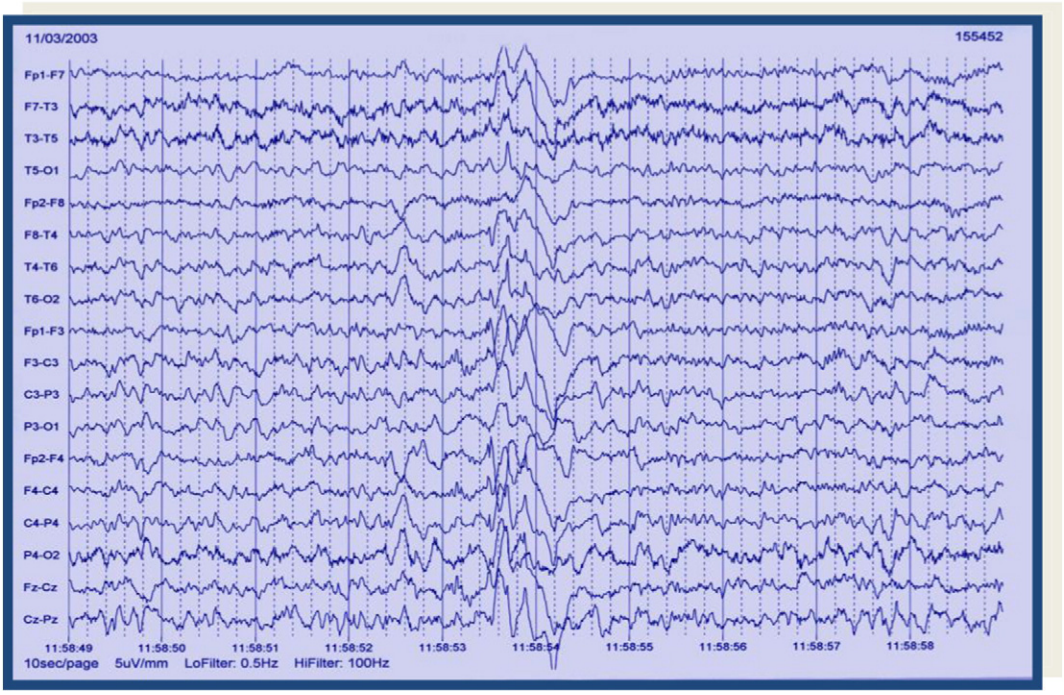

Fig. 2. EEG shows frequent paroxysmal generalized bursts of low amplitude spike-and-wave discharges bilaterally and synchronously with a background of diffuse 5–7 theta waves on both hemispheres.

of our patients had localized severe vermian atrophy. Therefore, the evaluation of the imaging findings of the current phenotype with different disease severity is recommended.

In autosomal recessive EPM1, 74% [21] of all probands show expanded repeats in both alleles of the cystatin B (*CSTB*) gene with more than 30 dodecamers, while normal alleles have only 2–3 copies. Other EPM1-associated *CSTB* mutations are rare and found in homo or compound heterozygote in 2% [22] of all probands. Progressive myoclonic epilepsy type 1 is transmitted in an autosomal recessive fashion and is linked to chromosome 21q22.3 [5]. The *CSTB* gene encoding cystatin B, a cysteine protease inhibitor, is the only gene known to be associated with EPM1 [23]. The largest allele recorded worldwide was 125 dodecamer repeats. The largest in our family was 120 repeats and was observed in the first patient. Despite outstanding advances, there is no convincing explanation of a direct relationship between genetic defects and the resulting clinical symptoms [6,24]. No detailed evaluation of phenotype–genotype correlation during the current era has been performed. However, we noticed that age at onset and severe

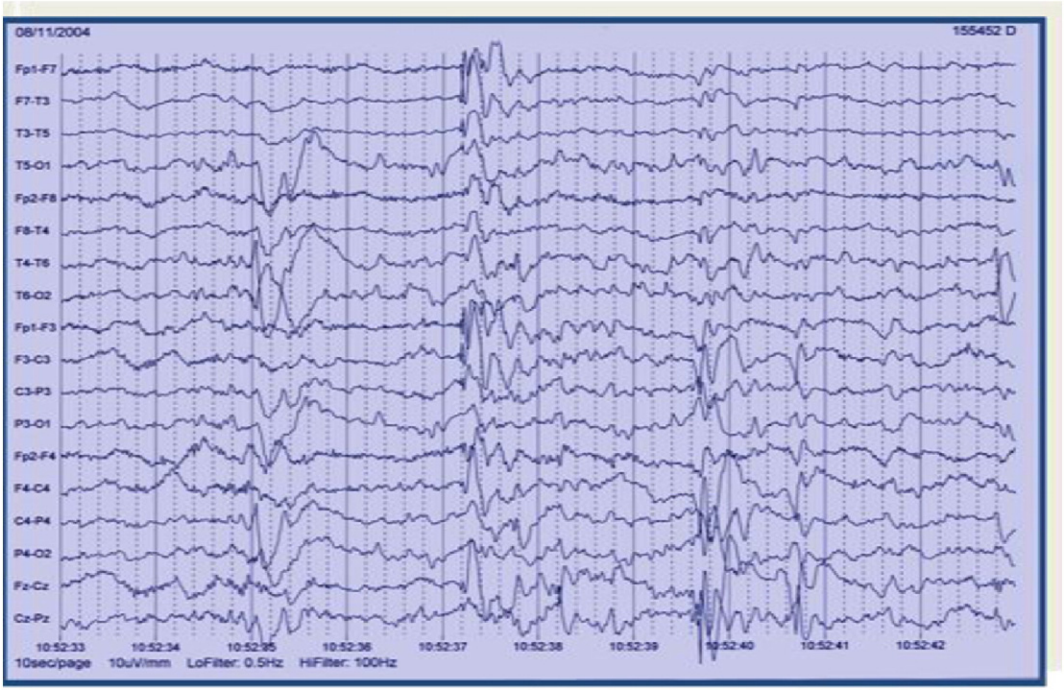

Fig. 3. EEG shows generalized polyspikes-and-slow wave complexes with slowing of the background of moderate amplitude (50–75 μV) and delta (2 Hz) and theta (5 Hz) particularly in the posterior regions.

myoclonus were earlier in all our patients and, particularly, with the largest repeat expansions. Cognitive impairment was also evident early in all, and the first two could not even initiate their normal primary education. The first patient is mentally retarded since his early childhood. The second patient had gradual deterioration of his cognition relatively early in the disease course and finally culminated in disability to continue his primary regular learning. The third patient had cognitive delay since the age of 9 years, and her IQ was 75 which put her in the category of borderline impairment. The fourth and fifth patients had IQs of 81 and 82, respectively, and this coincides with the low average category. Our patients, associated with classical dodecamer repeat expansion mutation, have a more severe form with early onset of myoclonus, generalized seizures, ataxia, motor and autonomic dysfunction, learning difficulty, cognitive impairment, brain atrophy, and recurrent notably viral infections. These findings may have important implications in revealing pathogenesis, and, therefore, it is important to achieve a more detailed evaluation of genotype–phenotype correlations. However, despite progress in understanding the biological function of *CSTB*, disease mechanisms in EPM1 remain elusive [6,25,26].

Pharmacotherapy is the cornerstone of management. There is no specific treatment. However, recent advances in antiepileptic drugs improved prognosis [27] significantly. Valproate is the first drug of choice, especially if started early [8]. It reduces myoclonus and frequency of generalized seizures. It was the first drug of choice in 80% and the only drug used in 20% of our patients. Levetiracetam is more effective when given early [5]. It showed substantial benefit in stimulus-evoked and action-induced myoclonus and generalized seizures [28–30]. It was the second drug of choice in 80% and the only drug used in 20% of our patients. Clonazepam as an add-on therapy is the only FDA-approved drug for myoclonic seizures [12,31]. We used it in 60% of our patients. Primidone and high-dose piracetam were beneficial in myoclonic seizures, and each was used in one of our patients. Piracetam was used only to treat myoclonus; however, we noticed that it exacerbated generalized tonic–clonic seizures. Topiramate and zonisamide were also used as add-on treatments [32]. Topiramate worsened the control of morning jerks and generalized seizures in one of our patients. Lamotrigine caused increased sleepiness, tremulousness, and incoordination in one of our patients. Brivaracetam, an SV2A ligand that differs from levetiracetam by its mechanism of action profile, showed significant antiepileptic activity in experimental models of epilepsy and myoclonus [33,34]. It is currently being investigated as an add-on treatment in adolescents and adults. Ketogenic diet was tried in one of our patients with no appreciable benefits. Vagus nerve [35] and subthalamic deep brain [36] stimulation have been reported to diminish generalized seizures and myoclonus, respectively.

Phenytoin should be avoided as it aggravates myoclonus and provokes cerebellar degeneration and atrophy. Carbamazepine, oxcarbazepine, tiagabine, vigabatrin, gabapentin, and pregabalin should be avoided as they may exacerbate myoclonus and myoclonic seizures [37]. Phenytoin and carbamazepine worsened myoclonus in 60% of our patients. However, both were used for not more than 2–4 months, which makes it unlikely that it affected clinical and radiological outcome. In settings of recurrent, massive myoclonus or status myoclonicus, loud noises and bright lights should be avoided, and the patient should be nursed in a quiet room. Intensive acute treatment includes intravenous use of lorazepam, clonazepam, diazepam, midazolam, valproate, and levetiracetam. Phenytoin and fosphenytoin should be avoided. General anesthesia is rarely needed.

In conclusion, our study emphasized a particular phenotype of this disease consisting of earlier disease onset, debilitating myoclonus, generalized seizures, prominent cognitive dysfunction and learning difficulty, and earlier onset and rapid progression of motor, cerebellar, and autonomic dysfunction, brain atrophy, and recurrent viral infections. Although, many of the individual components of this phenotype were discussed in the literature, this particular constellation in tout à fait was not previously coined; therefore, this is a peculiar phenotype, and further research may shed light on this issue.

Disclosure

The authors have nothing to disclose.

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