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Reassessment of phenytoin for treatment of late stage progressive myoclonus epilepsy complicated with status epilepticus

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Summary In order to find an effective treatment option for status epilepticus in progressive myoclonus epilepsy (PME), we reviewed the clinical course of 9 patients with PME. Initially, epilepsy was successfully treated with antiepileptics. However, it gradually became refractory to medication, and status epilepticus emerged 3—19 years after the onset of epilepsy. In these patients, status epilepticus in PME was classified into (1) myoclonic status epilepticus (MSE), (2) myoclonic-generalized status epilepticus (MGSE), and (3) generalized status epilepticus (GSE). MSE was common in patients with neuronal ceroid lipofuscinosis, and GSE was common in those with dentatorubral—pallidoluysian atrophy. MGSE was characterized by the mixture of escalating myoclonus and generalized seizures, and was observed in patients with Gaucher disease or unspecified PME. All patients were often refractory to infusion of benzodiazepines and barbiturates but phenytoin was able to terminate status epilepticus in 7 patients. Oral phenytoin administration as preventive therapy was effective in 6 patients. Aggravation of myoclonus was not provoked by these treatments. We propose that phenytoin should be considered as a treatment choice for PME patients at late stages to prevent the detrimental effects of prolonged or repeated status epilepticus on the brain tissues.

Introduction

Progressive myoclonus epilepsy (PME) represents an epilepsy syndrome characterized by myoclonic jerks, generalized seizures, mental retardation, and ataxia. This entity encompasses many hereditary neurodegenerative diseases, including neuronal ceroid lipofuscinosis (NCL),

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Table 1 Clinical features of the patients.

Patient	Sex	Age (years)	Diagnosis	Onset age of epilepsy	Seizure types during pre-status period	Effect of antiepileptics during pre-status period
1	F	27	LINCL	3 y	Tonic Myoclonic (4 y—)	Fair: VPA, CZP, AZM, TRH, CBZ
2	M	14	LINCL	3 y	Atonic, tonic—clonic Myoclonic (4 y—)	Fair: VPA, CZP, piracetam
3	M	14	MELAS/MERRF overlap	10 y	Clonic Myoclonic (13 y—)	Fair: ZNS, CZP, piracetam Poor: CBZ, PB
4	F	24†	Gaucher disease type 3	8 y	Tonic—clonic Myoclonic (12 y—)	Fair: VPA, CZP, AZM, NZP, ST Good: amniotic tissue implantation, DMSO
5	M	30†	Degenerative PME	7 y	''Generalized tremor'' Myoclonic (10 y—)	Fair: VPA, CZP, ZNS, CLZ, DZP, CBZ, AZM Poor: 5-HTP, ACTH, ketogenic diet
6	F	12†	Degenerative PME	3 y	Atonic Myoclonic (9 y—)	Good: ketogenic diet Fair: ACTH, CZP, PB, LZP Poor: VPA, PSL, AZM
7	M	25	Degenerative PME (sibling of patient 6)	1 y	Myoclonic Tonic—clonic (2 y—)	Good: VPA, LZP, γ-globulin Poor: TRH
8	M	34†	DRPLA	7 y	Tonic—clonic Myoclonic (7 y—)	Fair: PB, CBZ, VPA
9	M	11	DRPLA	4 y	Tonic—clonic Myoclonic (10 y—)	Good: VPA, CZP, PB

Good: seizure free for 3 months or more, fair: seizure free for less than 3 months, poor: no change. ACTH: adrenocorticotropic hormone, AZM: acetazolamide, CBZ: carbamazepine, CLZ: clorazepate dipotassium, CZP: clonazepam, DMSO: dimethyl sulphoxide, DRPLA: dentatorubral—pallidoluysian atrophy, DZP: diazepam, 5-HTP: 5-hydroxytryptophan, LINCL: late infantile type neuronal ceroid lipofuscinosis, MELAS: mitochondrial encephalopathy with lactic acidosis and stroke-like episodes, MERRF: mitochondrial encephalopathy with ragged red fibers, NZP: nitrazepam, PB: phenobarbital, PHT: phenytoin, PME: progressive myoclonus epilepsy, PSL: predonisolone, TRH: thyrotropin-releasing hormone, VPA: sodium valproate, ZNS: zonisamide.
† Deceased.

dentatorubral—pallidoluysian atrophy (DRPLA), Gaucher disease, mitochondrial encephalopathy with ragged red fibers (MERRF), Lafora disease, and Unverricht—Lundborg disease (ULD). Epilepsy in these disorders results from pathological processes specific to each entity such as an accumulation of neurotoxic materials at specific layers in the cerebral cortex (Frei and Schiffmann, 2002) and decreased numbers of inhibitory cortical interneurons (Hayashi et al., 2007). During the early phase of the illness, epileptic seizures are usually responsive to treatment with valproate, clonazepam, zonisamide (Kyllerman and Ben-Menachem, 1998; Yoshimura et al., 2001), and piracetam (Fedi et al., 2001), but often they gradually become refractory to these agents and develop repeated episodes of status epilepticus at advanced stages of the illness.

Phenytoin (PHT) is generally effective for the treatment of status epilepticus due to various conditions. However, aggravation of myoclonus as a side effect of PHT has been reported in generalized myoclonic epilepsies (Genton et al., 2000; Thomas et al., 2006). Neurological symptoms and life expectancy may also be worsened by PHT administration in ULD, partly due to its toxic effect on the cerebellar Purkinje cells (Eldridge et al., 1983). Nevertheless, in our experience, we have found that PHT is a safe and effective option for the management of epilepsy in PME sufferers at advanced stages. We demonstrate the evolution of epilepsy in PME patients and the effect of PHT for treatment of status epilepticus within this population.

Patients and methods

We identified 9 cases of PME (ages 11—34 years, M:F = 6:3; Table 1) where PHT had been used for the treatment of intractable status epilepticus that could not be terminated by bolus or continuous infusion of benzodiazepines or barbiturates. These patients had been diagnosed with late infantile NCL (LINCL) ($n = 2$), an overlapping condition of MERRF, and mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) ($n = 1$), Gaucher disease type 3 ($n = 1$), and DRPLA ($n = 2$). A specific diagnosis could not be reached in 3 patients despite extensive investigations. In patient 5, a muscle biopsy showed unremarkable results. A liver biopsy ruled out Lafora disease, and DRPLA and ULD were ruled out by genetic analysis. Patients 6 and 7 are siblings for whom a skin biopsy and gene analysis showed normal results for Lafora disease and DRPLA, respectively. A myelinoid body was identified