doi:10.1093/brain/awn007 *Brain* (2008), **131**, 818–828

POLG1 mutations cause a syndromic epilepsy with occipital lobe predilection

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The epileptic semiology of 19 patients (from 15 families) with mitochondrial disease due to mutations in the *POLG1* gene is presented. The patients were either homozygous for the 1399G>A (p.A467T) or 2243G>C (p.W748S) mutations or compound heterozygotes for these two mutations. While the clinical features have been reviewed, detailed analysis of their epilepsy is presented for the first time. Irrespective of genotype, patients developed an epileptic syndrome with initial features of occipital lobe epilepsy. Occipital seizure phenomena included flickering coloured light, sometimes persisting for weeks, months or even years, ictal visual loss, horizontal/vertical nystagmus or oculoclonus, dysmorphopsia, micro-/macropsia and palinopsia. Most patients developed simple partial seizure phenomena with motor symptoms suggesting frontal lobe seizure initiation or spread. Simple and complex partial seizures, clonic- and/or myoclonic seizures with epilepsia partialis continua and frequent convulsive status epilepticus were observed in this syndrome that appears to be a symptomatic and secondary generalized or multifocal epilepsy with focal occipital predilection. The mean age of seizure presentation was 18.4 years (6–58 years). All patients developed status epilepticus and 11 patient deaths were, all related to prolonged convulsive status epilepticus, including two with liver failure apparently precipitated by treatment with sodium valproate.

Keywords: epilepsy; *POLG*; mitochondrial disease; occipital lobe; status epilepticus

Abbreviations: SE = status epilepticus; C-/NC = convulsive/non-convulsive; SPS = simple partial seizure; CPS = complex partial seizure; PLEDS = periodic lateralized epileptic discharges; sGTC = secondary generalized tonic–clonic seizures; EPC = epilepsia partialis continua

Received September 27, 2007. Revised January 4, 2008. Accepted January 8, 2008. Advance Access publication January 31, 2008

Introduction

Epileptic seizures are a common feature of mitochondrial disease either caused by primary mitochondrial DNA (mtDNA) mutations or defects in nuclear genes that control mtDNA stability, such as the mitochondrial DNA polymerase γ, POLG. Mutations in the catalytic subunit of POLG (*POLG1*) produce a variety of neurological syndromes including progressive external ophthalmoplegia (PEO) (van Goethem *et al*., 2001), Alpers' syndrome (Nguyen *et al*., 2005, Ferrari *et al*., 2005) and a mitochondrial spinocerebellar ataxia-epilepsy syndrome (MSCAE) (Hakonen *et al*., 2005, Tzoulis *et al*., 2006). Epilepsy is one of the most common manifestations of *POLG1* disease, particularly with mutations affecting the spacer region (Winterthun *et al*., 2005; Horvath *et al*., 2006; Tzoulis *et al*., 2006).

Occipital lobe epilepsy is uncommon, but its low frequency may simply reflect the fact that the occipital cortex constitutes only about 10% of the total cortical area (Sveinbjornsdottir and Duncan, 1993; Aarli and Engelsen, 2000). Occipital lobe epilepsy may also be underrepresented in clinical samples due to the difficulties associated with precise localization of the lesions in many patients with focal epilepsy (Manford *et al*., 1992). The causes of occipital lobe damage resulting in epilepsy include peri-natal trauma, focal ischaemia, malformations, encephalitis and mitochondrial diseases such as MELAS

Table 1 Patient clinical and genetic details and clinical seizure phenomena

Patient	Sex	Genotype	Seizure onset (years)	CPS	SPS	Eye/head-deviation	Focal clonic or myoclonic	Sides (R/L)	GTC	SE	Seizures in SE	†
1	M	467/467	39	Yes	Yes	Yes; right	Yes	L&R	Yes	Yes	C & SP	+
2	F	467/467	19	Yes	Yes	NK	Yes	R&L	Yes	Yes	SP	
3	M	467/467	6	Yes	Yes	NK	Yes	L&R	Yes	Yes	C	+
4	F	467/467	16	Yes	Yes	NK	Yes	L	Yes	Yes	C & NC	
5	M	467/748	20	?	Yes	NK	Yes	L	Yes	Yes	C & SP	+
6	F	467/748	18	?	Yes	Yes; left	Yes	L	Yes	Yes	C	+
7	F	467/748	13	?	Yes	NK	Yes	L&R	Yes	Yes	C	+
8	F	467/748	14	?	Yes	NK	Yes	R&L	Yes	Yes	C	+
9	M	748/748	12.5	?	Yes	Yes; right	Yes	L&R	Yes	Yes	C	+
10	F	748/748	16	Yes	Yes	NK	Yes	L	Yes	Yes	C	
11	M	748/748	14	Yes	Yes	Yes: left	Yes	L&R	Yes	Yes	C & SP	+
12	F	748/748	10	?	Yes	NK	Yes	L	Yes	Yes	C	+
13	F	748/748	18	Yes	Yes	Yes; left	Yes	L	Yes	Yes	C	
14	F	748/748	15	Yes	Yes	NK	Yes	L&R	Yes	Yes	C	
15	F	748/748	17	No	Yes	Yes; left	Yes	L	Yes	Yes	C	
16	F	748/748	17.5	Yes	Yes	Yes; left	Yes	L	Yes	Yes	C & NC	
17	M	748/748	58	Yes	Yes	Yes; left	Yes	L	Yes	Yes	C	+
18	F	748/748	19	Yes	Yes	NK	Yes	R&L	Yes	Yes	NC	
19	F	748/748	8	?	Yes	Yes; left	Yes	L&R	Yes	Yes	C	+

Pt = patient; Debut = age of onset of epilepsy; CPS = isolated complex partial seizure; SPS = simple partial seizure; GTC = secondary generalized tonic clonic seizures; SE = status epilepticus; C = convulsive; NC = nonconvulsive; SP, simple partial status epilepticus. Sides = predominant or exclusive lateralization (could differ over time). ? = uncertain or not explicitly mentioned in notes or by patient. † = dead. NK = not known; i.e. either not observed or no reference to in patient notes/EEG recordings. Clonic and myoclonic seizures were differentiated on clinical grounds. Clonic seizures were slower, repetitive and often developed into epilepsia partialis continua. Myoclonic jerks were briefer, occasionally very local, but often involved variable muscle groups.

(Andermann *et al.*, 1986; Montagna *et al.*, 1988; Kuzniecky, 1998; Engelsen and Aarli, 1999).

We present the clinical epileptological features and EEG findings of a large cohort of patients with the A467T and W748S *POLG1* mutations in whom occipital epilepsy was the presenting feature of their epileptic syndrome. Epilepsy was present in 76% of all patients with these two mutations. It is an early and defining factor of the syndrome and carries a poor prognosis.

Patients and Methods

Nineteen patients were included in this study; 17 were admitted to Haukeland University Hospital, Bergen and 2 admitted to St Olav's Hospital, Trondheim. Clinical data from the patients included have been reported (Winterthun *et al.*, 2005; Tzoulis *et al.*, 2006). Only 19 patients are included, the remainder being excluded either because they did not have epilepsy or EEG data was unavailable. Eighteen of our patients had repeated routine EEG examinations and four patients had prolonged video-EEG recording. The patients were either homozygous for the 1399G > A (*p*.A467T) or 2243G > C (*p*.W748T) *POLG1* mutations or compound heterozygous for these two changes. Mutation analysis of the *POLG1* gene was performed as reported previously (Winterthun *et al.*, 2005).

Results

Clinical characteristics

Epilepsy was the presenting symptom in 12/19 and in seven of these it occurred together with a simultaneous vascular headache. In the other 7/19, clumsiness or ataxia was the presenting symptom. All patients with epilepsy had MSCAE. The clinical semiology and symptoms relevant to their epilepsy are presented in Table 1. The mean age of onset of epilepsy for all patients was 18.4 years. There were no significant differences in mean or median age of onset when comparing the three genotypes; A467T/A467T mean (years) ± SD 20 ± 13.8, median 17.5; A467T/W748S mean 16.3 ± 3.3, median 16; W748S/W748S mean 18.6 ± 13.5, median 16 [$P = 0.91$ for comparison of means (one way ANOVA), $P = 0.88$ for medians (Kruskal–Wallis)].

All of the patients had focal clonic or myoclonic seizures (Table 1), most often involving an arm, shoulder, neck and or head and manifesting usually as simple partial (SPS) motor seizures. Occasionally, persisting focal or generalized myoclonic jerks were observed. Nine of 19 patients had therapy refractory partial seizures with the perception of coloured or white light in one visual hemifield occurring daily for weeks, months or even years. The epileptic origin of these symptoms was substantiated by EEG examination showing increased focal occipital epileptic activity during periods of enhanced visual disturbances. Evaluation of any impaired consciousness during the prolonged focal motor seizures was difficult due to lack of continuous clinical monitoring. Complex partial seizures (CPS) with motor symptoms were confirmed in 11 patients. Ten of 11 patients had clear motor symptoms as part of their CPS (focal jerks, head turning, motor automatisms) and one patient had both motor and visual symptoms during their

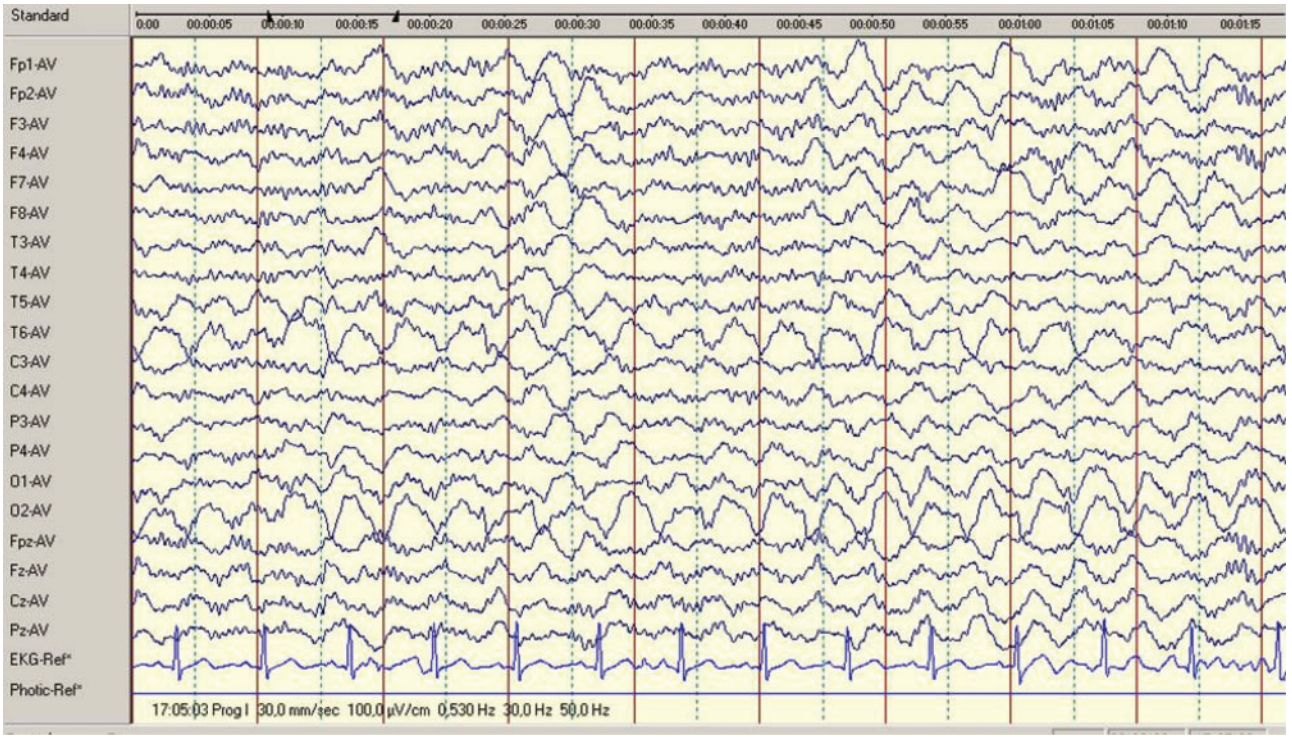

Fig. 1 Ictal videometry from patient I3 taken May 2005 (I/I260). Clinically there was jerking of the left arm and the patient gave neither verbal response nor eye contact. The EEG reveals general slowing and in electrodes T6 (O1) and O2 there are focal slowing and sharp waves that are suppressed by eye opening (data not shown). The EEG resembles slow occipital waves of youth.

CPS. In addition, one patient had an episode of CPS with visual symptoms classified as NCSE. The reporting of visual symptoms in CPS may be underreported. Classical frontal or temporal lobe-like CPS were seldom seen, and automatisms were very rare.

Motor SPS was sometimes accompanied by a clear epileptic EEG correlate, sometimes with rhythmic focal slowing of the contralateral, posterior hemispheric quadrant or occipital electrodes (Fig. 1). Initially, this was erroneously considered to be non-seizure-related EEG artefact, or motor-induced artefact. There was no clear correlation between frequency of focal clonic movements of arm-shoulder-head and frequency of occipital slow waves. Nevertheless, the EEG changes (Figs 1, 2, 4, 6 and 8) are considered epileptiform in nature. All 19 patients had GTC seizures, all considered secondary GTC (sGTC).

Clinical symptoms occurring as episodic or as distinct seizure phenomena suggestive of occipital lobe involvement are listed in Table 2. These symptoms corroborate previously reported occipital lobe seizure symptoms (Ludwig and Marsan, 1975; Salanova *et al.*, 1992; Williamson *et al.*, 1992; Sveinbjornsdottir and Duncan, 1993; Andermann and Zifkin, 1998; Kuzniecky, 1998; Aarli and Engelsen, 2000).

All patients had one or more episodes of status epilepticus (SE) (Table 1). In 6/19, SE was the presenting seizure phenomenon, whereas the median time from onset of epilepsy to the first SE was 2 months for the group as a whole. Four of the 13 female patients had SE during pregnancy. The number of convulsive SE (CSE) varied between one and nine episodes, lasting days or weeks, with the need for barbiturate anaesthesia in all patients with CSE. One patient (patient 18) had only non-convulsive SE (NCSE) and two other patients (patients 4 and 16) had also CSE as well as NCSE (Table 1).

EEG

We were able to access parts of or whole EEG tracings from 295 registrations from our 19 patients (Table 3, Figs 1–8). The maximum number of recordings in one patient was 29. The oldest EEG examined was from 1962, the most recent May 2007. We were able to follow the EEG changes over time in several patients, with both interictal and repeated ictal registrations and cerebral function monitoring (CFM) during intensive care unit treatment of SE. In four patients, five sessions of video-EEG recordings each lasting over 24 h were available.

EEG revealed early pathology with occipital slow wave and epileptic activity in the majority of patients (Table 3). In seven patients, the occipital rhythmic activity resembled occipital slow waves of youth with suppression on eye opening. There were, however, low amplitude spikes or sharp waves suggesting that this was indeed epileptic activity. Figures 1 (patient 10) and 2 (patient 13) show these typical ictal and interictal EEG findings.

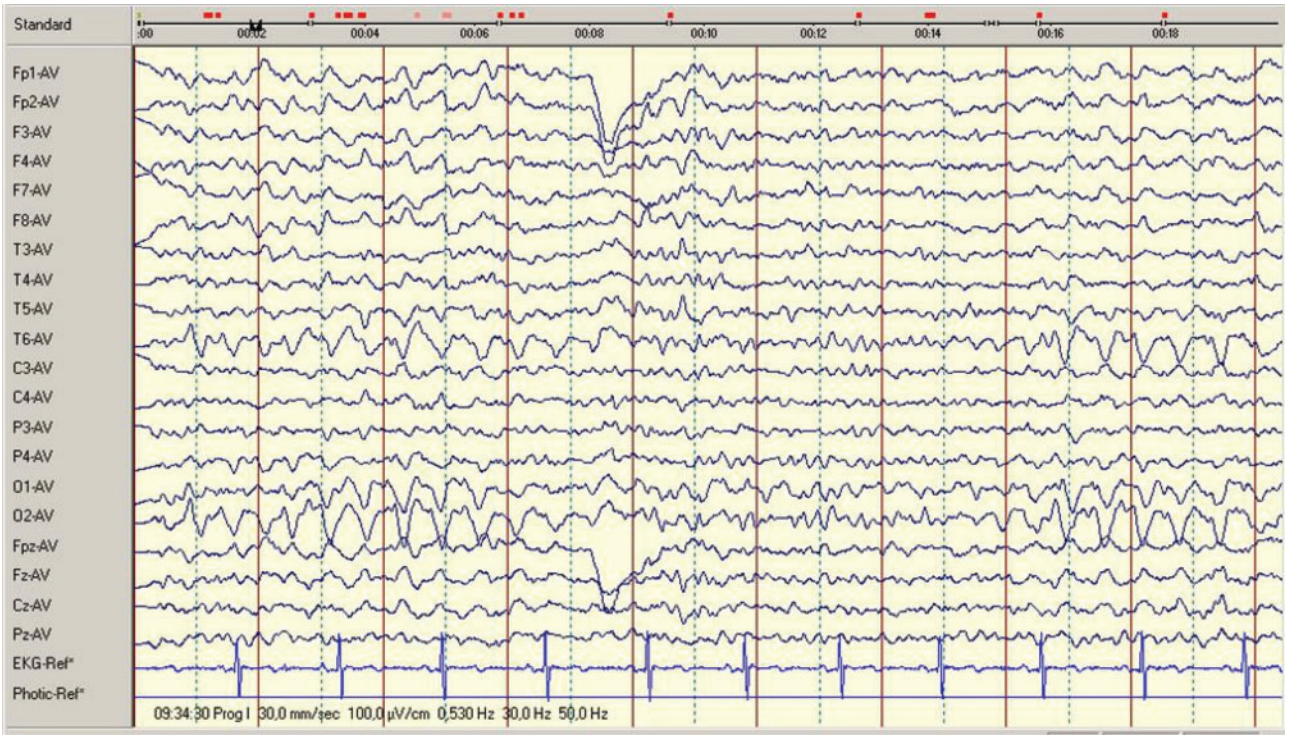

Fig. 2 Interictal EEG from patient I0 (4/0128) taken in 2004. Prior to this EEG she had had three secondary generalized tonic–clonic seizures on different occasions. The EEG shows focal slow-wave activity with sharp components in T6, O1 and O2 with suppression by eye opening. During seizures, epileptic activity was seen in O1 and O2 (data not shown).

Table 2 Transient or fluctuating occipital symptoms occurring as clinical seizure phenomena with or without EEG correlation

Patient	Occipital or occipito-temporal seizure phenomena	Headache	Emesis
1	Scotomas (up to a few hours)	Yes	Yes
2	Flickering light, white and intensified with colours in right hemi-field	Yes	Yes
3	Flickering white light to the left, visual loss and vertical nystagmus	**?**	
4	Visual loss, bilateral horizontal nystagmus	Yes	Yes
5	Micro-macropsia, dysmorphopsia, palinopsia, visual loss	Yes	Yes
6	Grey dots & visual loss, vertical nystagmus, eyelid myoclonus	Yes	Yes
7	Visual loss; hemianopsia	Yes	Yes
8	Visual loss and flickering coloured points 'to the right'	Yes	Yes
9	Black points in left hemi-field	Yes	Yes
10	Blinking points to the right, visual loss, left sided horizontal nystagmus	Yes	Yes
11	Visual loss, left sided horizontal nystagmus	Yes	Yes
12	Blue-yellow flickering light, left sided horizontal nystagmus	Yes	Yes
13	Flickering light, transient visual loss, amaurosis	Yes	Yes
14	Flickering coloured points, yellow, rose, vertical nystagmus	Yes	Yes
15	Flickering coloured lights in left hemi-field	Yes	Yes
16	Ictal visual loss; e.g. total amaurosis for days	Yes	Yes
17	Oral automatisms, rotatory nystagmus	Yes	?
18	Flickering lights perceived in the midle of the visual field	No	No[a]
19	Transient hemianopia, nystagmus, flower-bouquet in visual field	Yes	Yes

Yes and No refer to ascertained information in the clinical notes. **?**, explicit information lacking, but most likely the symptoms did occur.
[a]Had both symptoms during a period of impaired liver function prior to transplantation.

No correlation between frequency of clonic jerks and the rhythmic EEG frequency could be seen. Differently structured occipital, or occipito-temporal ictal epileptic activity is shown in Figs 3 (patient 14) and 4 (patient15), and the full ictal-interictal spectrum is contained in Figs 1–8.

Generalized slowing of cerebral activity was seen in many of the EEG recordings, both inter- and post-ictally,

Table 3 EEG abnormalities in the patients with POLG and epilepsy

Patient	Focal abnormality	Epileptic activity	MRI—occipital lesions	Psw-EEG	Occipital Epileptic activity	*n*
1	Yes	Yes	R		No	14
2	Yes	Yes	B	+	L>R	24, 2v
3	Yes	Yes	N	+	R>L	16
4	Yes	Yes	N	+	R>>L	29
5	Yes	Yes	R		R	9
6	Yes	Yes	ND	+	L>R (t-occ)	22
7	Yes	Yes	N		L>R	16
8	Yes	Yes	B	+	R>L	17
9	Yes	Yes	B	+	L>R	15
10	Yes	Yes	L		R>L	5
11	Yes	Yes	B	+	R>L	18
12	Yes	Yes	N	+	R>L	25
13	Yes	Yes	L		R>L	2; Iv
14	Yes	Yes	B	+	R>L	6, Iv
15	Yes	Yes	R	+	R>L	18, Iv
16	Yes	Yes	B	+	R	24
17	Yes	Yes	N		R (fr-t-occ)	2
18	Yes	Yes	N		R	4
19	Yes	Yes	NA	+	L>R	29

All the patients had generalized abnormalities in their interictal EEGs. Focal abnormality = slowing or focal paroxysmal activity with or without epileptic activity. MRI—occipital lesions; R = right sided; L = left sided; B = bilateral; N = normal; NA = not available; ND = not done; Psw-EEG = polyspike wave activity: i.e. at least one EEG with 2 or more distinct spikes or sharp waves followed by a distinct slow wave; + = presence of psw; > = More than, i.e. *bilateral*, but at least in some registrations clear dominance of one side; t-occ = tempero-occipital; fr-t-occ = fronto-tempero-occipital; *n* = number of EEG recordings; v = Video EEG (>24 h).

however, all but one patient revealed clear focal occipital, or regional occipito-temporal epileptic activity in at least one registration. Most patients had consistent interictal occipital slowing and epileptic activity over several years. Ictal registrations revealed either severe general slowing, with or without epileptic activity, or, as in the majority of patients, consistent focal occipital, or temporo-occipital, epileptic discharges occurring in T5, T6, O1 and O2 electrodes.

One patient (1) had no focal occipital epileptiform EEG activity. In 13 of the remaining 18 patients, there was a right occipital or right dominant bi-occipital epileptic activity, while left predominant activity was seen in five patients. In most patients ($n = 15$), the occipital epileptic EEG activity could be correlated with clinical signs or symptoms of occipital lobe involvement (Table 2). Fourteen patients showed bilateral occipital epileptic activity, although most of these EEG's revealed a distinct lateralization that was substantiated by subsequent EEG. Distinct bilateral, synchronous occipital epileptic EEG activity was seen at least once in four patients. At least 12/19 patients had polyspike wave components in at least one of their EEG's.

Suppression of slow and epileptic occipital epileptic activity by eye opening was seen in the ictal and inter-ictal EEG's of several conscious patients at different times (e.g. Figs 2 and 8) and might be an early EEG characteristic. Epileptic activity could be suppressed briefly by eye opening, even several years after onset of the epilepsy. It is not possible to estimate of the frequency of this, however, due to inconsistent reporting during EEG registration.

Frontal or more generalized epileptic activity was associated with more generalized motor seizure phenomena, or a focal frontal motor seizure semiology. Clinical correlate included eye or head turning, focal clonic or myoclonic jerks, or more regional motor seizure symptoms such as clonic movements of an arm, shoulder, neck, face and hemiclonic seizures. Only during prolonged focal seizures in SE did two patients reveal transient EEG abnormalities consistent with the more classic periodic, lateralised epileptic discharges (PLED's) (not shown). In one patient with frequent myoclonic jerks, lateralized frontal continuous spiking was observed (EEG from 1981; not shown).

Anti-epileptic medication

Most patients received combination therapy. In the majority of patients, prevention of sGTC was achieved with sodium channel blockers at least for a period of time, e.g. with carbamazepine (CBZ), phenytoin (PHT), oxcarbazepine (OXC) or lamotrigine. Often these drugs were combined with a benzodiazepine. Topiramate was effective against myoclonic activity in one patient, while gabapentin increased focal myoclonic activity in two patients and lamotrigine caused the same in one of them. Phenobarbital was effective in one patient. Sodium valproate was associated with liver failure in five patients and should be avoided (Tzoulis *et al.*, 2006). Six of the 11 patients who died had used valproate, although one had used this drug for over 16 years prior to a terminal liver failure. One female patient continued valproate treatment after successful liver transplantation (patient 18). Nine of the 11 patients who died used or had used clonazepam (CLP), with some effect against myoclonus. Of the surviving eight patients, seven used carbamazepine ($n = 5$) or oxcarbazepine ($n = 2$), four used lamotrigine and four used or still use clobazam (CLB). All who have used clobazam are still alive. Two living patients are treated with levetiracetam.

Other pharmacological treatments included; lorazepam ($n = 1$), ethosuximide ($n = 1$) and progesterone ($n = 1$). Corticosteroids ($n = 3$) and azothioprine ($n = 1$) used in patients in whom vasculitis was suspected, had no effect on their condition or epilepsy. One patient was treated with ketogenic diet, and one with plasmapheresis, without effect.

Cerebral imaging

At least one cerebral MRI was performed in 17/19 patients; one patient (6) never had MRI performed and one MRI

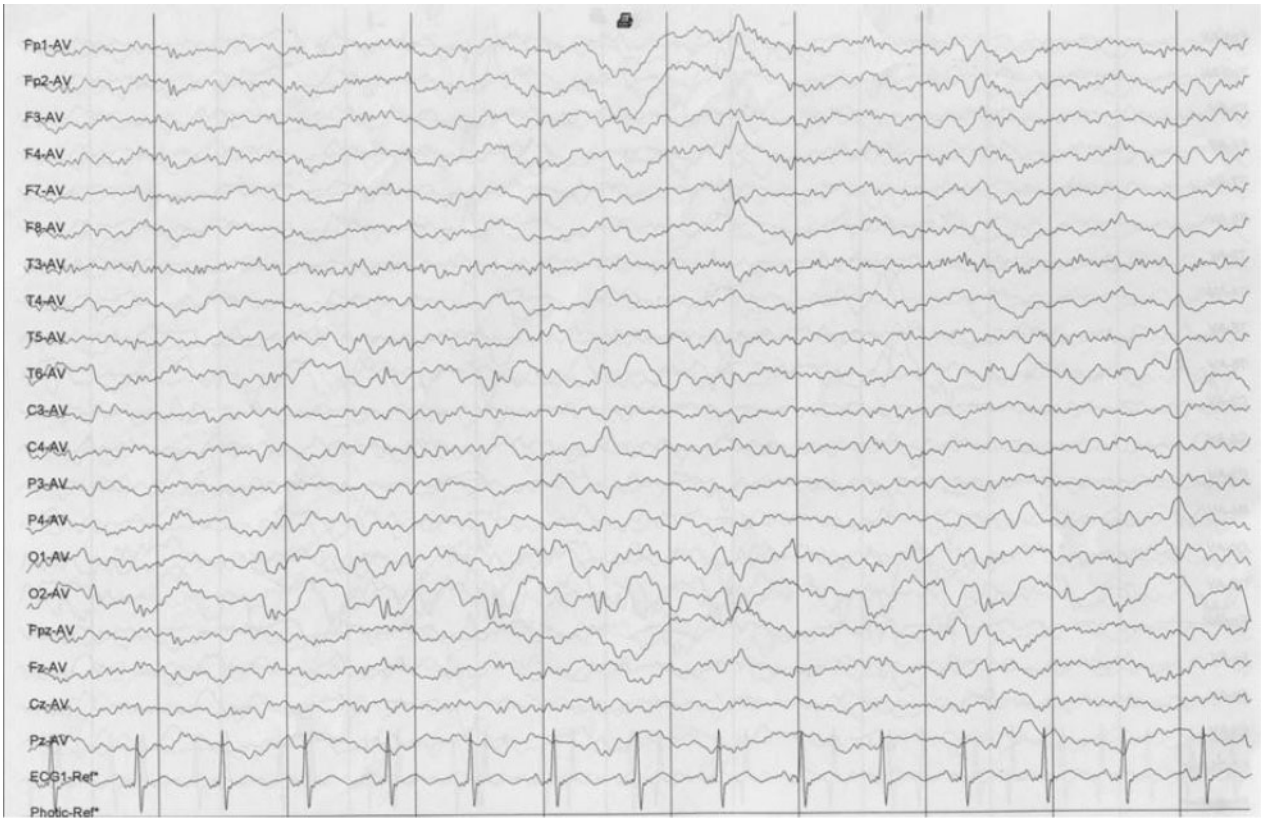

Fig. 3 Ictal EEG from patient 14 (1/2185) taken 1999. She had serial generalized tonic–clonic seizures, headache and flickering white spots in left hemifield. The EEG reveals generalized slowing with focal sharp waves in T6 and O2, the right temporo-occipital electrodes.

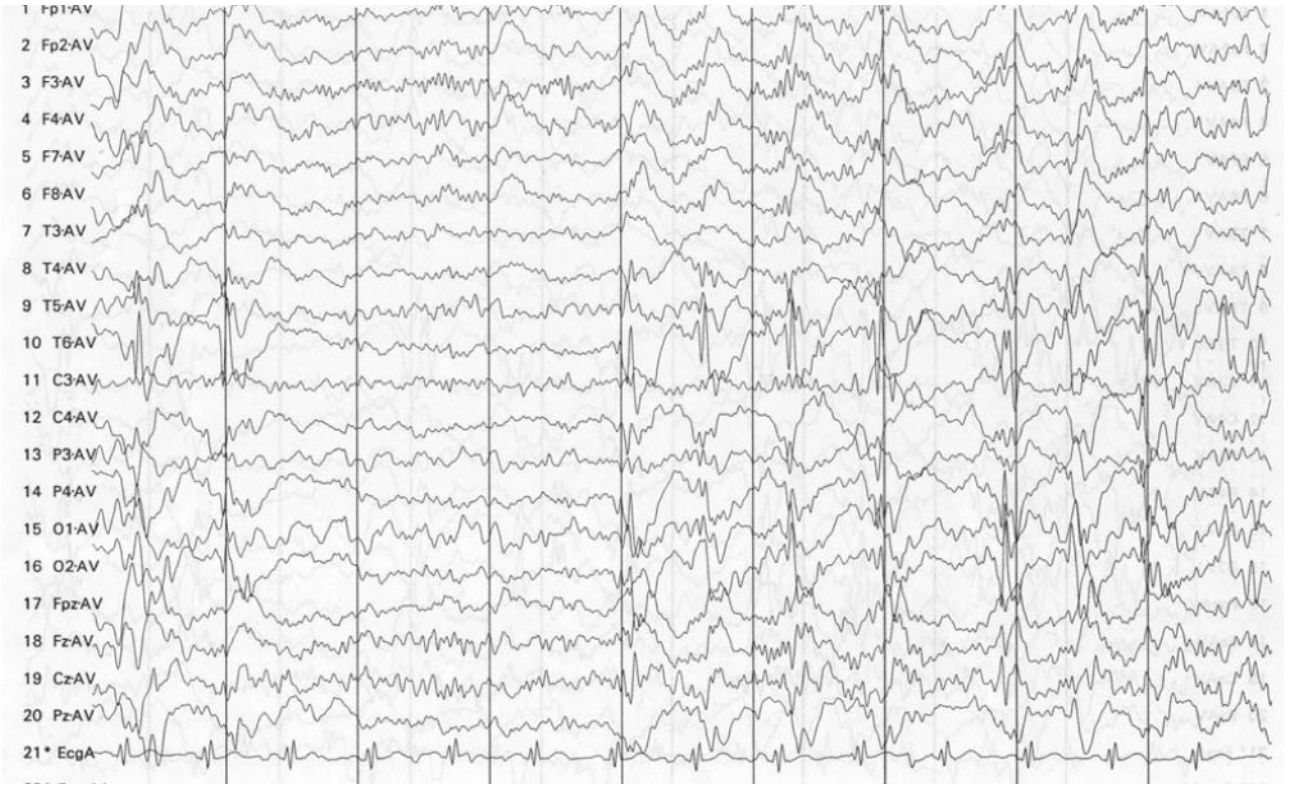

Fig. 4 Ictal EEG from patient 15 taken in 1995 (2/2499). The patient experienced simple partial SE with flickering coloured light in left hemifield, followed by generalized tonic–clonic seizures and focal motor status. The EEG again shows general slowing with focal sharp waves in T6 and O1/O2. These changes are suppressed by eye opening.

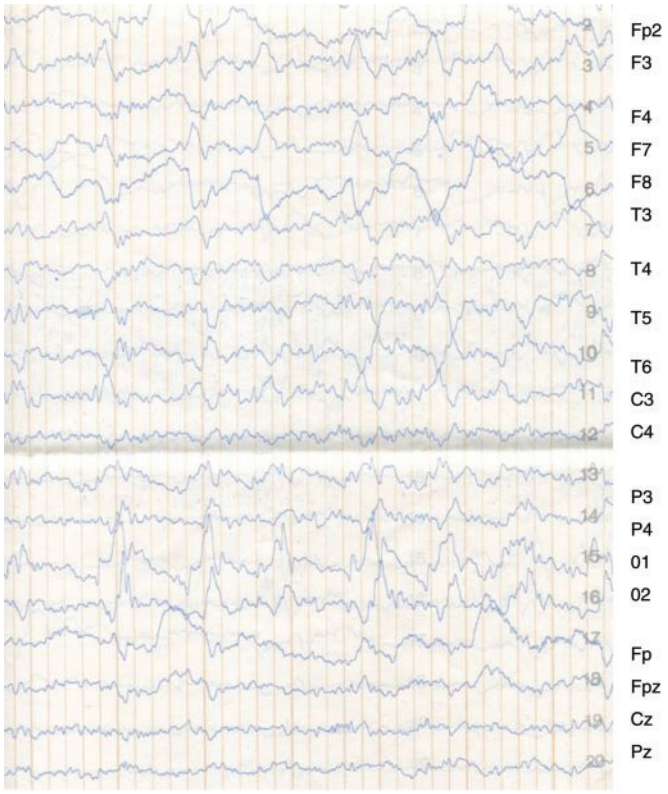

Fig. 5 Ictal EEG from patient 16 taken in 1984 (1/2847). She had complex partial seizures, left-sided headache and ongoing reduced vision. The EEG shows focal epileptiform activity in both occipital electrodes. Lead 15 = left occipital electrode; Lead 16 = right occipital electrode.

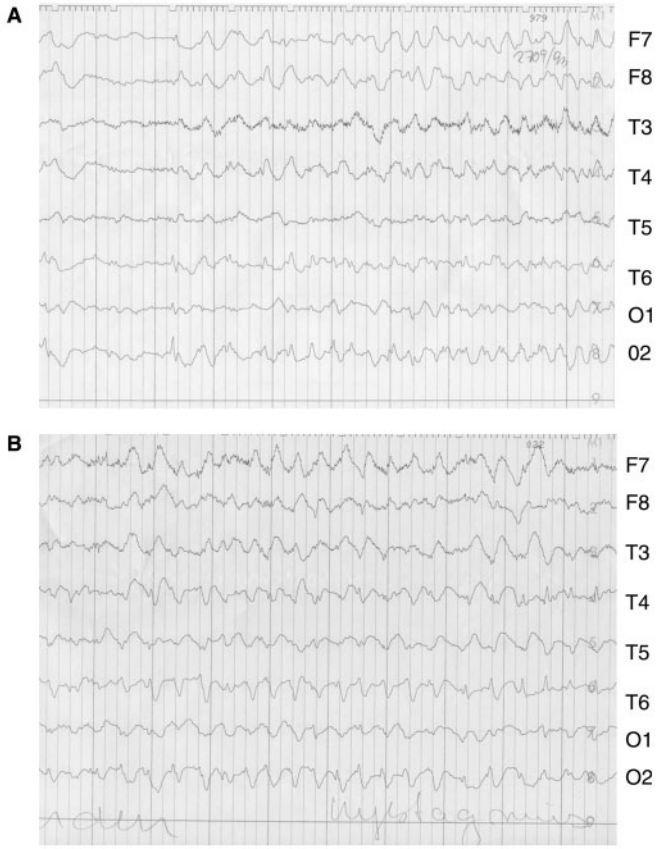

Fig. 6 (**A**) Ictal EEG in patient 16, taken in 1993 (6/2709). She was found at home 'confused' and thought to be post-ictal. Following admission she had repeated focal seizures with head turning to the right, nystagmus and head jerks. Prior to this EEG she had 100 mg diazepam and 950 mg phenytoin. This eight-lead ictal EEG reveals generalized slowing and occipital sharp-wave components with right occipital amplitude dominance. (**B**) Same EEG as (a). During ictal nystagmus the sharp wave components increase in the right temporo-occipital electrodes (leads 6 and 8).

is unavailable to us (19). One patient had a normal MRI early in the disease while all others had abnormalities detectable from the first investigation. Focal T2 high signal intensity changes were seen affecting, in order of decreasing frequency, the thalamus (12/17), occipital cortex (11/17), deep cerebellar structures (7/17), extra-occipital cortex (6/17) and inferior olivary nuclei of the medulla oblongata (5/17). Atrophy of the cerebellum (9/17) and the cerebrum (6/17) were also seen.

MRI studies were performed at various stages over many years, and not always related to episodes of epilepsy. The information available to us, therefore, varied considerably. It is possible, however, to make some statements concerning the correlation of images and epileptic phenomena, either recorded or observed. Eighteen of 19 patients had EEG changes involving the occipital lobes, but only 11/17 had occipital changes visible on standard MRI (Fig. 9A). Occipital lobe changes could vary with time and could regress, but not disappear. Five of the six patients with bilateral occipital lesions also had bilateral EEG findings and focal motor manifestations. Patient 16 had bilateral occipital lesions on MRI, but only right-sided EEG activity with left-sided jerks. Correlation between unilateral occipital lesions and EEG or clinical activity was more inconsistent. For example, patients 10 and 13 had left occipital lesions and bilateral, but right dominated EEG activity, and epileptic jerks involving the left side of the body. Six patients had occipital EEG foci and well correlated, bilateral or contralateral motor jerks, but with no occipital lesions on MRI. In two patients with persisting focal motor seizures involving the neck and arm (EPC), MRI showed evolving contralateral frontoparietal lesions (Fig. 9B).

Although thalamic high signal lesions were the commonest MRI abnormality detected (Fig. 9A), no correlation between epilepsy type or episodes of status and these lesions could be established. Cerebral atrophy was seen to accelerate after periods of severe epileptic exacerbation, either in the form of repeated episodes of generalized SE, or long periods of EPC. Cerebellar and cerebral atrophy could be clinically correlated with ataxia and cognitive decline, respectively. A detailed study of imaging findings in *POLG1* disease is currently in progress.

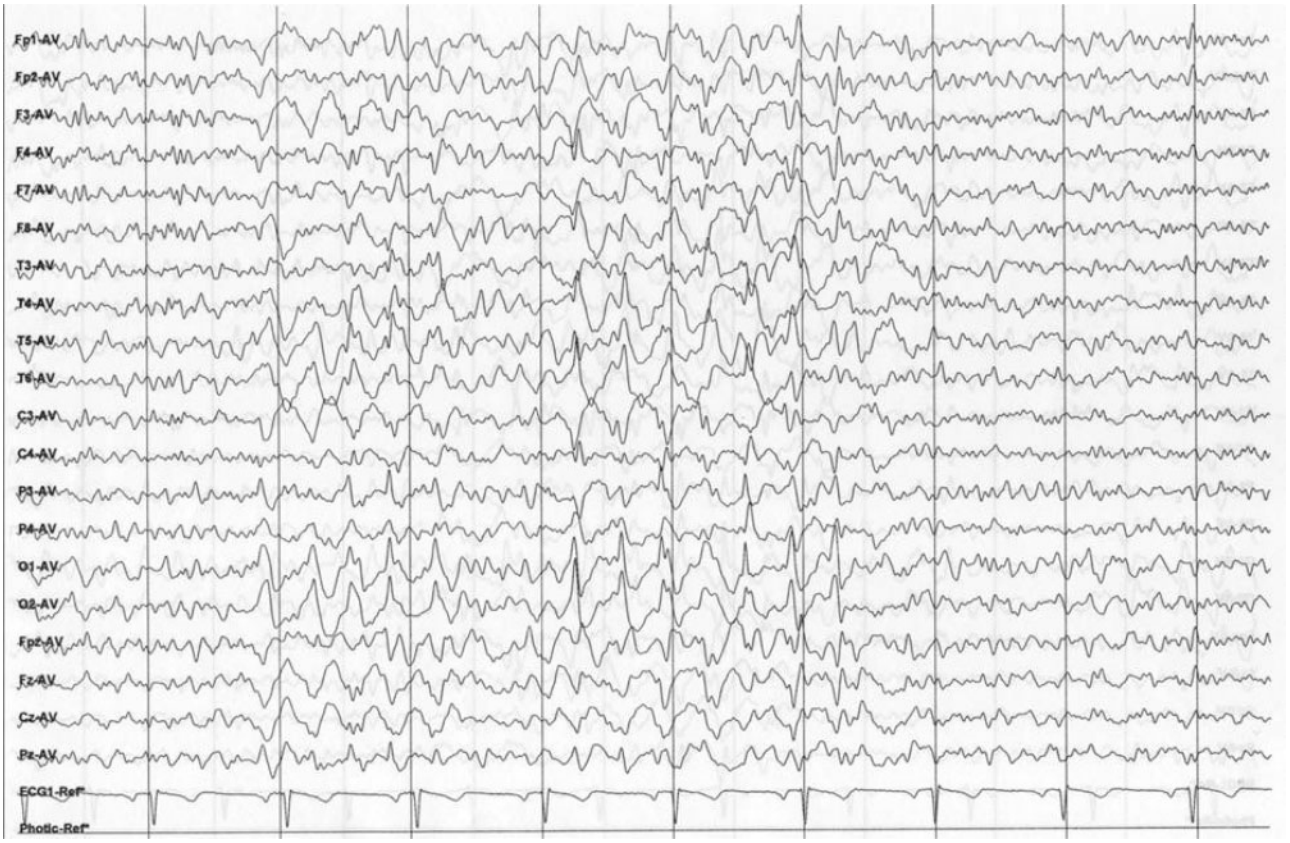

Fig. 7 Interictal EEG from patient 3 taken in 1998 (16/2208b), shortly after status epilepticus and two secondary generalized tonic–clonic seizures. There is paroxysmal slowing with sharp waves having a bilateral temporo-occipital localization and possible right amplitude dominance.

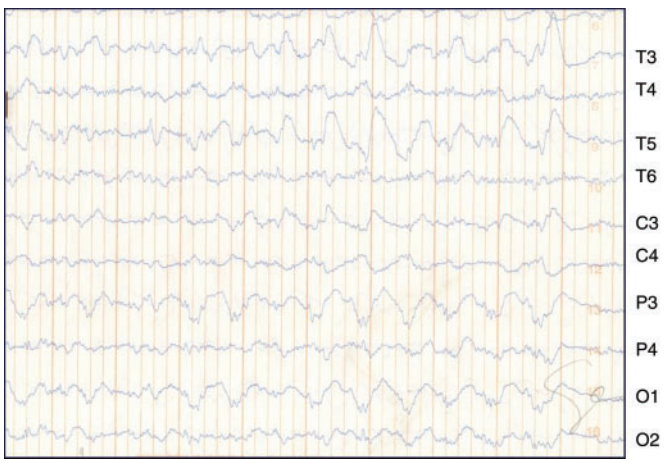

Fig. 8 Ictal EEG from 1986 in patient 7 (8/2750). She had a right homonymous hemianopia, myoclonic jerks in right arm and nystagmus. There is left temporo-occipital epileptic activity with transient suppression on eye opening.

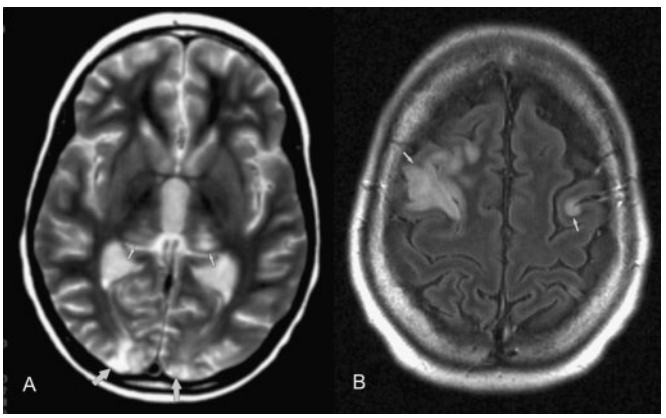

Fig. 9 (**A**) Axial T2-weighted MRI showing high signal lesions in the thalami (small arrows) and occipital cortices (large arrows). (**B**) Axial FLAIR MRI showing high signal intensity changes in the frontal cortex bilaterally (arrows) in a patient with focal motor status epilepticus.

Discussion

We present the clinical and electrophysiological findings in a large cohort of patients with the A467T and W748S *POLG1* mutations. Epilepsy is very common in MSCAE caused by *POLG1* mutation and develops 76% of all patients. Analysis of our whole material (33 patients) shows that the prevalence of epilepsy by genotype is—A467T: 100%, W748S: 70%, A467T/W748S: 75%. The seizure semiology, clinical findings, EEG and MRI data support the notion that the pathological process underlying

the epilepsy has an early predilection for the occipital lobes. Thereafter, patients develop what we suggest is an epileptic syndrome that always includes simple partial motor seizures; complex partial seizures and myoclonus are also very common and these patients have frequent episodes of SE. Repeated seizure activity, particularly SE, contribute to worsening mitochondrial function and energy deficiency that in turn often leads to a fatal outcome.

Clinical seizure semiology

Occipital symptoms occurred in all our patients and were an early feature (Table 2). Positive visual phenomena ranged from simple flickering light to formed visual hallucination (patient 19). Negative phenomena include scotomata, hemianopia and amaurosis. Nystagmus and eyelid myoclonus were also seen. Simple visual hallucinations with or without movement or flickering lights/colour and visual loss are established occipital lobe seizure phenomena (Penfield and Jasper, 1954; Ludwig and Marsan, 1975; Williamson *et al.*, 1992; Sveinbjornsdottir and Duncan, 1993). Even prosopagnosia, achromatopsia and the sensation of movement without detectable eye motion may be triggered from the occipital lobes (Sveinbjornsdottir and Duncan, 1993). Nystagmus or oculoclonic movements, detected by subdural EEG recordings or following occipital cortical stimulation, have been reported as occipital symptoms (Penfield and Jasper, 1954; Salanova *et al.*, 1992; Sveinbjornsdottir and Duncan, 1993), as have eyelid flutter and forced blinking (Sveinbjornsdottir and Duncan, 1993). In addition, eye deviation and headache with vomiting may have an occipital origin (Sveinbjornsdottir and Duncan, 1993; Andermann and Zifkin, 1998), as can hemiclonic seizures (Andermann and Zifkin, 1998) and contra-versive seizures (Rosenbaum *et al.*, 1986; Sveinbjornsdottir and Duncan, 1993).

All the symptoms recorded in Table 2 were correlated with epileptic activity in EEG, except palinopsia in patient 5. This symptom may be ictal, non- or post-ictal in nature (Lefebre and Kolmel, 1989). Similarly, amaurosis may be an ictal or post-ictal symptom.

EEG changes

Eighteen of 19 patients revealed focal or regional occipital epileptic activity corroborating the clinical symptoms of an occipital focus. In patients with occipital lobe epilepsy, regional rather than focal epileptiform activity is usually seen in scalp EEG (Salanova *et al.*, 1992; Williamson *et al.*, 1992; Kuzniecky, 1998). This is confirmed in our patients with most ictal EEG's revealing regional epileptic activity in electrodes T6/T5, often with amplitude dominance in O2 and O1. In addition, frontal and generalized epileptic activity occurred in most patients during seizure spread or SE. The EEG data are consistent, therefore, with the definition of the epilepsy as a symptomatic (or secondary) generalized epilepsy with occipital predilection.

Occipital lobe predilection

The occipital predilection remains a mystery. Whether striate cortical neurochemistry differs from other regions or the occipital lobes are more vulnerable remains to be established. In the waking state, the occipital cortex is among the most active sites in the brain due to the constant requirement for visual input, making it potentially vulnerable to injury by energy deficiency. Why this does not hold true for all mitochondrial diseases, however, is unclear, although in primary mitochondrial syndromes, heteroplasmy may also play a role.

While MRI changes involving the occipital lobes were frequent, not all patients had identifiable lesions on imaging, despite having an occipital EEG focus, at least initially. One possible explanation for this lack of correlation is that the MRI studies were not always performed in synchrony with the development or exacerbation of the epilepsy. It is also possible that the epileptic focus does not initially generate changes detectable using standard sequences. Further studies are therefore required together with the use of other imaging modalities such as spectroscopy and PET since these may help to detect early lesions that standard MRI misses.

Treatment of the epilepsy

Epilepsy is the single most important factor influencing morbidity and mortality in these patients. Patients deteriorated significantly and irreversibly after a periods of repeated severe seizures or SE. Moreover, MRI showed accelerated cerebral and cerebellar atrophy after such periods. Epileptic seizures and, to a much greater degree CSE, pose a significant energy demand to neurons, which the defective mitochondrial function presumably cannot meet. The resulting neuronal energy deprivation and ultimately neuronal injury and death in turn predispose to further seizures. While this theory may explain the severity, long duration, refractoriness and grave consequences of the seizures in our patients, it fails to explain what initiates the epileptic episodes. Nonetheless, it highlights the absolute requirement for rapid seizure control and aggressive treatment of break-through seizures since they signify a risk of CSE.

For *preventive* seizure control, most patients seem to benefit from the combination of a sodium channel blocker and a benzodiazepine; thirteen patients have used CBZ, mostly with some lasting effect and two patients using OXC are still alive. Eleven of 19 patients have used PHT, of which two are still alive, and this drug was used in most of the patients to control SE. It has proven necessary to titrate oral doses to high serum levels of PHT, e.g. 100–120 μM (reference; 40–80 μM) to control seizures, and of course,

this may contribute to unwanted long-term side effects in already ataxic patients. CLP as well as CLB has proven valuable adjuncts in most patients. Levetiracetam and topiramate have been effective, but experience with these is limited. The use of sodium valproate should be avoided at all costs, although it is of interest to note that one patient was able to continue valproate treatment after a liver transplantation. Some anti-convulsants appear to increase the myoclonus, e.g. lamotrigine and gabapentin, although whether this is the case in all patients is not clear from our data. Currently, we have had some success using a combination of PHT and CLP, although the benefit must be balanced against side effect such as sedation. The severity of this disorder and particularly the high risk of SE, necessitates close follow-up. We advocate aggressive treatment of infections and fever, good nutrition and particularly close follow-up during any pregnancy since four of our patients developed SE during pregnancy.

Break-through seizures need to be treated aggressively, since they frequently culminate in CSE. We have generally adhered to the EFNS guidelines (Meierkord *et al.*, 2006) for treatment of CSE and so-called refractory status epilepticus. Rapid use of diazepam or CLP, is followed by an infusion of phos-phenytoin (phenytoin is no longer registered for i.v. use in Norway). We aim to achieve serum levels of 100–120 μM, as a guideline, and levels are checked daily in patients with ongoing seizures. In therapy refractory SE, we use barbiturate anaesthesia with Thiopental, although we have also had good experience with Propofol which may terminate seizures more rapidly than Thiopental. We have limited experience with Phenobarbital, which might seem an interesting alternative to phenytoin in some patients, and intravenous levetiracetam and lorazepam that are not registered in Norway. One patient was unsuccessfully treated with electromagnetic stimulation.

Prognosis

The great majority of patients who died did so following prolonged periods of repeated CSE. Terminal multiorgan failure and/or liver failure, particularly following exposure to valproate, were also significant contributory factors. Earlier studies showed that the survival time was significantly shorter in compound heterozygotes (A467T/W748S) than patients homozygous for theA467T or W748S mutations (Tzoulis *et al.*, 2006). The same trend is seen in the current study. The median survival time for all patients in this study, regardless of mutation, was 8 years following the onset of epilepsy (data not shown). This highlights the need for close follow-up and lifelong anti-epileptic treatment in those who develop epilepsy.

Acknowledgements

We would like to thank colleagues at the Haukeland University Hospital, particularly Dr Håvard Skeidsvoll, for help in monitoring the patients during episodes of status epilepticus. We would also like to thank Jan H. Aarseth for help with the statistical analysis. Grants used for the research projects are gratefully acknowledged from Helse Vest, HF.

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