Recessive twinkle mutations cause severe epileptic encephalopathy

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The C10orf2 gene encodes the mitochondrial DNA helicase Twinkle, which is one of the proteins important for mitochondrial DNA maintenance. Dominant mutations cause multiple mitochondrial DNA deletions and progressive external ophthalmoplegia, but recent findings associate recessive mutations with mitochondrial DNA depletion and encephalopathy or hepatoencephalopathy. The latter clinical phenotypes resemble those associated with recessive POLG1 mutations. We have previously described patients with infantile onset spinocerebellar ataxia (MIM271245) caused either by homozygous (Y508C) or compound heterozygous (Y508C and A318T) Twinkle mutations. Our earlier reports focused on the spinocerebellar degeneration, but the 20-year follow-up of 23 patients has shown that refractory status epilepticus, migraine-like headaches and severe psychiatric symptoms are also pathognomonic for the disease. All adolescent patients have experienced phases of severe migraine, and seven patients had antipsychotic medication. Epilepsia partialis continua occurred in 15 patients leading to generalized epileptic status in 13 of them. Eight of these patients have died. Valproate treatment was initiated on two patients, but had to be discontinued because of a severe elevation of liver enzymes. The patients recovered, and we have not used valproate in infantile onset spinocerebellar ataxia since. The first status epilepticus manifested between 15 and 34 years of age in the homozygotes, and at 2 and 4 years in the compound heterozygotes. The epileptic statuses lasted from several days to weeks. Focal, stroke-like lesions were seen in magnetic resonance imaging, but in infantile onset spinocerebellar ataxia these lesions showed no predilection. They varied from resolving small cortical to large hemispheric oedematous lesions, which reached from cerebral cortex to basal ganglia and thalamus and caused permanent necrotic damage and brain atrophy. Brain atrophy with focal laminar cortical necrosis and hippocampal damage was confirmed on neuropathological examination. The objective of our study was to describe the development and progression of encephalopathy in infantile onset spinocerebellar ataxia syndrome, and compare the pathognomonic features with those in other mitochondrial encephalopathies.

Keywords: Twinkle; IOSCA; epileptic encephalopathy

Abbreviations: DWI = diffusion weighted images; IOSCA = infantile onset spinocerebellar ataxia; SLE = stroke like episodes

Introduction

Infantile onset spinocerebellar ataxia (IOSCA) (OMIM #271245) is a progressive neurodegenerative disease, which is caused either by homozygous (Y508C) or compound heterozygous (Y508C and A318T) C10orf2 mutations (Nikali et al., 2005; Hakonen et al., 2007). C10orf2 codes for the mitochondrial (mt)DNA helicase Twinkle, which works in close connection with mtDNA polymerase
gamma (POLG, POLG1) in mtDNA replication. Disorders caused by either C10orf2 or POLG1 mutations share clinical phenotypes. Recessive POLG1 mutations cause clinical entities varying from an infantile hepatocerebral ataxia, (Alpers syndrome, OMIM #203700) (Ferrari et al., 2005; Nguyen et al., 2005), to a mitochondrial spino-cerebellar ataxia-epilepsy syndrome (MSCAE), also called MIRAS (mitochondrial recessive ataxia syndrome) (Hakonen et al., 2005; Tzoulis et al., 2006). The combination of early encephalopathy, sensory axonal neuropathy, epilepsy and hepatopathy with mtDNA depletion in the liver was found in our compound heterozygotes, and the three patients with another recessive Twinkle mutation, T457I. This clinical presentation resembles POLG1 associated Alpers syndrome (Hakonen et al., 2007; Sarzi et al., 2007). IOSCA and MSCAE syndromes share clinical features, but spino-cerebellar degeneration manifests earlier and progresses faster in IOSCA (Koskinen et al., 1994b; Lonnqvist et al., 1998; Hakonen et al., 2007). Refractory epilepsy with occipital lobe predilection is common in MSCAE with the A467T and W748S POLG1 mutations (Engelsen et al., 2008).

We report on cerebral manifestations in IOSCA, ranging from migraine-like headaches and psychotic episodes to severe epileptic encephalopathy. We also present neuroradiological findings during and after status epilepticus, and neuropathological findings related to prolonged epileptic statuses in our patients.

## Patients and Methods

### Patients

Our material consists of 23 IOSCA patients: 21 patients homozygous for the Y508C mutation and two compound heterozygotes (Y508C and A318T). All patients, except patient 1 (Table 1), who died in 1998 before our follow-up started, have been examined and followed-up at the Division of Child Neurology of the Helsinki University Central Hospital, Helsinki, Finland. We have reported on the clinical course and neuropathological findings in IOSCA earlier (Koskinen et al., 1994a,b, 1995a,b; Lonnqvist et al., 1998). It has become evident that epileptic encephalopathy, psychiatric symptoms and migraine are important manifestations of the disease after childhood. In the following section, we summarize briefly the clinical course and findings in IOSCA, which we have reported earlier.

The clinical findings are identical in the homozygotes and compound heterozygotes, but the symptoms appear earlier and progress faster in the compound heterozygotes (Patients 22 and 23 in Table 1). The first symptoms—ataxia, muscle hypotonia, atethoid movements and loss of deep tendon reflexes—were first seen around the age of 1 year in the homozygous patients and at 6 months in the compound heterozygotes. Ophthalmoplegia and hearing deficit developed soon after the onset of the disease, and sensory axonal neuropathy and female hypogonadotropic hypogonadism by teen age. The heterozygotes lost even their ability to crawl by the end of the first year, while 18 of the homozygotes learned to walk independently or with a walking-aid, but became wheelchair bound by adolescence. All homozygous patients communicated with sign language. Although the patients’ primary capacity was normal, all had learning difficulties. The patients with an unsuccessful early rehabilitation were moderately mentally retarded in adolescence, while the patients with a proper rehabilitation and education were mildly retarded. All routine laboratory and metabolic screening tests, including plasma and cerebrospinal fluid (CSF) lactate, were normal in the homozygous patients (Koskinen et al., 1994b). Mild elevation of serum and CSF lactate, and an intermittent elevation of liver transaminases and a-fetoprotein was detected in the compound heterozygotes (Hakonen et al., 2007). Muscle morphology revealed only mild neurogenic atrophy. The biochemical or histochemical COX (cytochrome c oxidase) activity was slightly diminished in the compound heterozygotes. The structure and amount of mtDNA was normal in muscle (Koskinen et al., 1994a; Nikali et al., 2005; Hakonen et al., 2007). The spino-cerebellar degenerative changes—the moderate atrophy of the brain stem and the cerebellum, and the severe atrophy in the dorsal roots, the posterior columns and the posterior spino-cerebellar tracts—were uniform in IOSCA (Lonnqvist et al., 1998; Hakonen et al., 2007).

### Methods

We present clinical and radiological follow-up data on epilepsy, migraine and psychiatric symptoms in 23 IOSCA patients. The patients were clinically examined by one of us (T.L., formerly T.K.) between 1 and 2 year intervals. EEG was recorded 1–5 times on patients with seizures (18/23 patients) during and/or after status epilepticus. Three patients without epilepsy

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**Table 1 The psychiatric symptoms and epilepsy in infantile onset spinocerebellar ataxia**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Psychiatric symptoms</th>
<th>Age at onset of epilepsy (yrs)</th>
<th>Status epilepticus (number)</th>
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<tr>
<td>1 m</td>
<td>–</td>
<td>30</td>
<td>1</td>
<td>30⁰</td>
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<tr>
<td>2 f</td>
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<td>48</td>
</tr>
<tr>
<td>3 m</td>
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<td>30</td>
<td>6</td>
<td>41</td>
</tr>
<tr>
<td>4 f</td>
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<td>41</td>
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<td>26</td>
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<td>26⁰</td>
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<td>12⁰</td>
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<td>39</td>
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<td>–</td>
<td>2</td>
<td>5</td>
<td>4.5⁰</td>
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</table>

Patients 1–21 = homozygotes; patients 22–23 = compound heterozygotes. Yrs = years; m = male; f = female; + = medication for psychiatric symptoms; – = no or minimal psychiatric symptoms; ne = no epilepsy.  
⁰ Age at death.

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were imaged in order to assess the development of supratentorial brain atrophy. Diffusion weighted images (DWI) with apparent diffusion coefficient (ADC) were available in two patients (Patients 3 and 19 in Table 1). The images were performed 4 days (Patient 19) and 2 weeks (Patients 3) after the onset of status epilepticus. Autopsy findings of five patients are re-evaluated. Histopathological and immunohistochemical methods have been described in detail in our previous reports (Lonnqvist et al., 1998; Hakonen et al., 2007).

Results

Migraine and psychiatric symptoms

All adolescent IOSCA patients have had episodes of migraine-like headache. Severe generalized headache preceded epileptic seizures in some cases, but attacks of migraine with nausea, vomiting and lethargy appeared independently, too. The severity of the attacks and the intervals between the migraine episodes varied in individual patients and between patients.

Poor sleep and nocturnal restlessness was common in young IOSCA-patients, but psychiatric symptoms requiring treatment appeared gradually during adolescence. The patients became tearful and somnolent, or agitated with uncontrolled rage attacks. They could, for example, crash into furniture or other people with their wheelchair. Seven patients had medication for their symptoms (Table 1). We have used selective serotonin reuptake inhibitors (SSRI) and antipsychotic medication (older neuroleptics, risperidone or olanzapine) with a cautious dosage in the beginning. Five patients were treated by psychiatrists communicating with sign language. According to the psychiatrists, the episodes fulfilled diagnostic criteria of psychosis and three patients were diagnosed with schizophrenia. The episodes recurred, lasted from several days to weeks, and the severity of the attacks increased. The severity of the attacks and the intervals between the migraine episodes varied in individual patients and between patients.

Epilepsy

Eighteen patients had seizures, which developed into an epileptic encephalopathy in 15 (65%) of them. The process started at the ages of 2 and 4 years in the compound heterozygotes and between the age of 15 and 34 years (mean = 24 years) in the homozygotes. The seizures manifested as myoclonic jerks or focal clonic seizures and progressed to epilepsy partialis continua in 15 patients and further to a generalized status epilepticus in 13 of them (Table 1).

The episodes recurred, lasted from several days to weeks, and the symptoms fluctuated between epilepsy partialis continua and generalized tonic clonic seizures. Discomfort, abdominal pain, vomiting, migraine-like headache, restlessness or agitation preceded the onset of the epileptic status. The seizure episodes were often precipitated by stressful events like infections or surgery. The onset of epilepsy indicated progression of the disease with loss of the ability to walk or stand supported, or even to sit in a wheelchair. Some patients recovered slowly over several months without regaining their previous condition. Their muscle hypotonia and weakness increased, they had difficulties in swallowing and fatigued easily. The first IOSCA-patient with status epilepticus (Patient 4 in Table 1) is 41-years old, lives in a nursing home for severely disabled persons and has survived 11 epileptic statuses during the past 18 years. The death of eight patients was directly or indirectly related to epilepsy. The time from the first seizures to death varied from 1 month to 5 years.

Three IOSCA-patients have had seizures of a different kind (Table 1). A 12-year-old female (Patient 6 in Table 1) had a generalized convulsion and a complex partial seizure. Her EEG showed background abnormality and a temporal slow wave focus. She was on carbamazepine therapy for 6 years and at the time the medication was discontinued, her EEG was normal. She remains seizure-free at her present age of 39. A 13-year-old boy (Patient 18) had daytime absences, and an 11-year-old boy (Patient 20) had short nocturnal tonic seizures. Their interictal EEG recordings showed no epileptogenic activity and both are seizure free on antiepileptic medication (oxcarbazepine) at ages of 22 and 16 years, respectively.

Drug treatment

Conventional antiepileptic drugs have been ineffective in most of our patients. We initially treated the patients with prolonged epileptic status with barbiturate anaesthesia but the results were poor. The seizures continued, and the treatment was complicated with pneumonia or a urinary tract infection. Early treatment, with benzodiazepine infusion, especially midazolam, was occasionally effective. Evaluation of liver enzymes (alanine aminotransferase or ALAT 232 units/l, ref. 10–35 U/l, and γ-GT 160 U/l, ref. 5–50 U/l), and icterus with elevated bilirubin levels (total: 224 μmol/l, ref. 5–25 μmol/l, conjugated: 160 μmol/l, ref. 1–8 μmol/l) was detected in patient 4 (Table 1) 1 month after initiation of valproate medication. A similar elevation of transaminases was detected also in Patient 7 (Table 1). As valproate was discontinued, icterus disappeared and the liver enzymes normalized in both patients. Phenytin or phenytoin were ineffective and caused an elevation of the liver enzymes. Oxcarbazepine had some effect on the seizures, but hyponatremia was a troublesome side effect. Some patients benefited from lamotrigine or levetiracetam.

EEG findings

The EEG was initially normal in all patients, but the frequency of background activity decreased with advancing age (Koskinen et al., 1994b). Focal continuous or periodic discharges with slowing of the background activity were seen during epilepsy partialis continua and the discharges became generalized during the status epilepticus. The epileptic activity often continued for weeks with fluctuation between these two states. Periodic lateralized epileptiform discharges (PLEDs) were common (Fig. 1A and B). The background activity was progressively abnormal after each epileptic status (Fig. 2A).

MRI findings

We have described the sequence of MRI findings from cerebellar cortical to olivopontocerebellar and finally to spinocerebellar atrophy (Koskinen et al., 1995b). The supratentorial findings—cortical
oedema and later cortical and central atrophy—appeared at the time and after the onset of epilepsy. The cortical oedema was of a non-vascular distribution. The oedematous area varied from multiple small cortical lesions to the involvement of the whole hemisphere, thalamus and caudate nucleus (Fig. 1C). In diffusion weighted imaging (DWI, \( b = 1000 \)), the lesions showed restricted diffusion 4 days after the onset of status epilepticus [Patient 19, Fig. 1D, thus behaving like early ischemic changes with decreased apparent diffusion coefficient (ADC) values]. The ADC values were normal or slightly increased 2 weeks after the onset of the insult (Patient 3, Fig. 2B). Some of these lesions were reversible. However, widening of the ventricles and sulci, consistent with atrophy, developed (Fig. 3). Supratentorial cortical and central atrophy was seen in all patients with intractable status epilepticus, but not in patients without refractory epilepsy (Fig. 4).

**Neuropathology**

We discuss the supratentorial neuropathological findings in patients 5, 8, 14, 16 and 22 (Table 1). Patients 5 and 14 died...
**Figure 2** EEG and MRI of a male patient (Patient 3 in Table 1) 2 weeks after the onset of his last epileptic status at the age of 41. (A) Remarkable slowing of the EEG after status epilepticus. (B) Left: a T₂-weighted MR image showing acute lesions with increased signal intensity on the right hemisphere and atrophy of the left hemisphere 3 months after a status epilepticus. Middle: a diffusion weighted trace image with increased signal intensity on the right side. Right: apparent diffusion coefficient map showing resuming signal intensity on the right hemisphere after acute ischaemia.

**Figure 3** (A) A T₂-weighted image of a 34-year-old male patient (Patient 9 in Table 1) with status epilepticus. There are multiple oedematous lesions on both hemispheres. (B) A T₂-weighted image 30 days after recovery. The oedematous lesions have resolved, but widening of the CSF spaces indicates development of atrophy.
3 months after the onset of seizures during an intractable epileptic status at the ages of 26 and 21 years, respectively. Their supratentorial findings were mild without significant cortical changes. Patient 8 died at the age of 24 years, 4 years after the onset of epilepsy at the end of an epileptic episode lasting 8 weeks. He had patchy cortical laminar necrosis, also the thalami and subthalamic nuclei were affected. The amygdala and especially the left hippocampus showed epileptogenic sprouting of the granular cell axons into the inner molecular layer (Fig. 5C and D). Patient 16 died of pneumonia at the age of 21 years, 5 years after the onset of epilepsy. She had been bedridden and unable to communicate since her first status epilepticus. She had parieto-occipital cortical atrophy in both parasagittal watershed regions and the most severe laminar cortical necrosis was seen on the medial surface of both visual cortices (Fig. 5A and B). Reduction of the white matter caused a mild central atrophy with dilatation of the lateral ventricles. Patient 22, a heterozygote, died in a month after the onset of epilepsy. Severe ischemic changes throughout the cerebral cortex, basal ganglia and thalami had been detected neuroradiologically and were histologically confirmed (Fig. 6) (Hakonen et al., 2007).

**Discussion**

At the time of our very first report (Koskinen et al., 1994b) all IOSCA patients but one were alive, the oldest at the age of 34 years. The severity and consistency of cerebral symptoms—migraine-like headaches, psychotic episodes and catastrophic epilepsy was not evident at that time. Today most of our patients have epilepsy, which has directly or indirectly caused the death of eight of them. The development of epilepsy has not been predictable the same way as the spinocerebellar degeneration of the disease. The atrophy of the sensory and cerebellar pathways and corticospinal degeneration progress steadily with age, but the age of onset of epilepsy has been highly variable and a few patients have been spared of epilepsy altogether. Our oldest patient, whose brother died during a status epilepticus at the age of 30, is now 48 and has not had seizures. The other symptoms besides epilepsy progressed equally in both siblings. The role of external factors in the development of epilepsy can only be postulated. Malaise and discomfort experienced by our patients before the onset of seizures may indicate presence of a metabolic derangement. There is increasing evidence of the role of free radicals in development of symptoms in mitochondrial diseases. Their role may be especially significant in the development of epilepsy, since seizures are known to increase the production of free radicals, which again induces more seizures (Kovacs et al., 2002; Liang and Patel, 2006). Thus an isolated seizure in a patient with already compromised mitochondrial function may lead to a vicious circle and catastrophic situation as we have seen in our patients and what others have described in association with other mitochondrial disorders.

New mechanisms behind neurodegeneration in mitochondrial diseases have been revealed recently. One of these concerns mitochondrial movement. Mitochondria are dynamic organelles, which migrate, divide and fuse, and through these processes ensure
metabolite and mtDNA mixing. This activity has been shown to be crucial for the mitochondria and disturbances in these dynamic functions has shown to be an important cause in neurodegeneration (Knott et al., 2008).

We and collaborators have recently reported complex I (CI) deficiency and mtDNA depletion in IOSCA. MtDNA depletion was detected in the frontal cortex and cerebellum, and to a lesser extent also in the liver. MtDNA deletions or point mutations were not detected. IOSCA can therefore be included in the group of tissue-specific mtDNA depletion syndromes (Hakonen et al., 2008).

In vitro studies have shown normal helicase function in the IOSCA (Y508C) mutant Twinkle, while a defective helicase activity was described in the T457I mutant (Sarzi et al., 2007). This may explain the neonatal onset and fatal Alpers-like hepatoencephalopathy in the latter patients. The molecular mechanism behind the brain-specific mtDNA depletion in IOSCA cannot be explained by current knowledge.

Stroke-like episodes (SLE), migraine, psychiatric symptoms and epilepsy are common in MELAS, one of the most common mitochondrial disease (Feddersen et al., 2003; Iizuka and Sakai, 2005), and occur also in POLG-related recessive ataxia syndromes (Hakonen et al., 2005; Horvath et al., 2006; Deschauer et al., 2007). Stroke-like lesions with high signal intensity on T2-weighted images are typical MRI-findings in MELAS. These lesions usually decrease in size and intensity over time and may resolve or reappear in a new location or develop in an area of atrophy or altered cortical signal intensity (Iizuka et al., 2003).

Similar lesions, sometimes reaching massive dimensions and encompassing the whole cortex, subcortical white matter and basal ganglia in one hemisphere were seen in our patients, too.

Diffusion weighted images (DWI), especially apparent diffusion coefficient (ADC) maps are used to differentiate between vasogenic and cytotoxic oedema. DWI (b = 1000, trace) show hyperintensity in both instances, while ADC maps show hyperintensity in vasogenic oedema and hypointensity in cytotoxic oedema typical for ischemia. Diffusion weighted images in IOSCA maps showed hyperintensity, and ADC maps were hypointense in the acute phase, but later turned normal or hyperintense indicating that the process was of ischemic nature. The ADC maps in MELAS patients are normal or mildly hyperintense, which is more consistent with vasogenic than with cytotoxic oedema (Michelson and Ashwal, 2004). Identical vasogenic oedema is seen in the posterior reversible leucoencephalopathy syndrome (PRES) with parieto-occipital predominance (Bartynski, 2008). POLG mutations with occipital predilection in MRI and EEG share features with PRES (Engelsen et al., 2008). The importance of timing of the DWI is evident and should be taken into account when evaluating the pathomechanism of the stroke like lesions.

Epilepsia partialis continua was first described in MELAS, but it is emerging as one of the important clinical features indicating mitochondrial dysfunction in the brain (Canafoglia et al., 2001; Van Goethem et al., 2003; Tzoulis et al., 2006; Deschauer et al., 2007). The neuropathological findings are characterized
by foci of necrosis, predominantly localized in the cerebral cortex and in the hippocampus—a highly epileptogenic area (Michelson and Ashwal, 2004). Similar supratentorial post-mortem findings, related to the duration and number of epileptic statuses before death, were found in IOSCA, too. Generalized seizures and myoclonias are the typical seizure manifestations of MERRF (mitochondrial encephalopathy with ragged red fibres) and the neuropathological lesions involve preferentially inferior olivary

Figure 6 A male patient (Patient 22 in Table 1). (A) MRI before the onset of status epilepticus. (B) CT at the onset of status epilepticus with focal clonic seizures in the left arm and leg. Note the hypodense lesion in the right basal ganglia (arrow). (C) CT 2 weeks later during the generalized and prolonged status epilepticus.
nucleus, the cerebellar dentate nucleus, the red nucleus and the pontine tegmentum, structures implicated in the genesis of myoclonus (Kunz, 2002). Presumably the myoclonic jerks in IOSCA are caused by the degenerative changes in the inferior olivary nucleus, pons and cerebellar dentate nucleus. The causal relationship between epilepsy and laminar cortical necrosis with hippocampal damage in mitochondrial disorders is far less clear (Iizuka et al., 2006).

Syndromic epilepsy with occipital lobe predilection has been described in the mitochondrial spinocerebellar ataxia-epilepsy syndrome (MSCAE) (Engelsen et al., 2008). Visual symptoms were common in epilepsy in MSCAE, but such phenomena could not be detected in IOSCA. The epilepsy in IOSCA showed no focal predilection, but focal jerking from one side of the body often progressed to a generalized status epilepticus making epilepsy partialis continua with generalization characteristic to IOSCA. Periodic lateralized epileptiform discharges (PLED) are described during status epilepticus in MELAS and other mitochondrial disorders (Michelson and Ashwal, 2004), and were seen also in IOSCA. Conventional antiepileptic drugs are generally ineffective in mitochondrial encephalopathies, especially in epilepsy partialis continua and prolonged statuses associated with SLE and tissue damage (Kunz, 2002). Valproate and barbiturates may impair respiratory chain activity and should be avoided in all mitochondrial disorders (Finsterer, 2006), and valproate is known to precipitate fatal liver failure in patients with recessive POLG1 mutations (Horvath et al., 2006; Tzoulis et al., 2006; Engelsen et al., 2008). We used valproate on two patients before the mitochondrial aetiology of IOSCA was known, but fortunately avoided fatal complications by discontinuing the treatment. The best option for intravenous therapy has been midazolam as a continuous infusion at the onset of the status epilepticus. We have used oxcarbazepine and/or levetiracetam added with clonazepam for a variable time after prolonged epileptic statuses.

Psychiatric symptoms, mainly depression, has been reported in mitochondrial diseases (Finsterer, 2006; Fattal et al., 2007). One may argue that reactive depression after the diagnosis of a severe progressive disease should not be counted as a symptom of the disease itself. Similarly uncontrolled rage-attacks in some of our patients could be counted as a normal reaction in a situation, where cognitive functions are relatively spared, but ways of expressing oneself are severely limited. However, the attacks fulfilled diagnostic criteria of a psychotic episode, and psychiatrists and psychotherapists able to communicate with sign language and proper medication were helpful in treating our patients.

IOSCA syndrome shares features with other mitochondrial recessive ataxia syndromes (Table 2). The somatosensory system conveying proprioceptive information to the brain and cerebellum is similarly affected in IOSCA and Friedreich’s ataxia (Lonnqvist et al., 1998). IOSCA patients do not have cardiomyopathy, and ophthalmoplegias, hearing deficit, cognitive impairment, psychiatric symptoms and epilepsy are rare or not existing in Friedreich’s ataxia (Pandolfo, 2008). Mitochondrial spinocerebellar ataxia-epilepsy syndrome (MSCAE) also called MIRAS (mitochondrial recessive ataxia syndrome) share clinical features with IOSCA, but the spinocerebellar degeneration manifests earlier and progresses faster in IOSCA (Hakonen et al., 2005; Engelsen et al., 2008). Tissue specific mtDNA depletion is detected in IOSCA and in Alpers syndrome, but the degenerative changes in the liver and the gliosis and spongiform atrophy of the brain are far more severe in Alpers syndrome (Ferrari et al., 2005; Hakonen et al., 2007).

The mtDNA helicase Twinkle-associated epileptic encephalopathy share many features with other syndromic epilepsies with mitochondrial aetiology. These symptoms and signs should alert the clinician to consider a form of mitochondrial encephalopathies, even if the laboratory tests typical for mitochondrial disorders remain negative.

### Acknowledgements

We thank the patients and their families for the participation in the study.

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**Table 2 The clinical features and findings in infantile onset spinocerebellar ataxia, Friedreich's ataxia, Mitochondrial spinocerebellar ataxia-epilepsy syndrome and mtDNA polymerase gamma-Alpers**

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<td>Cardiomyopathy</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>(+)</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>++</td>
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<tr>
<td>Psychiatric symptoms</td>
<td>+</td>
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<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>++b</td>
<td>–</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Liver involvement</td>
<td>+ c</td>
<td>–</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>MRI</td>
<td>Spinal cord atrophy</td>
<td>++</td>
<td>++</td>
<td>+</td>
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<tr>
<td></td>
<td>Brain stem atrophy</td>
<td>++</td>
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<td>+</td>
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<tr>
<td></td>
<td>Cerebellar atrophy</td>
<td>++</td>
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<td>+</td>
</tr>
<tr>
<td></td>
<td>Stroke-like lesions</td>
<td>++</td>
<td>–</td>
<td>++</td>
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<tr>
<td></td>
<td>Supratentorial brain atrophy</td>
<td>+</td>
<td>(+)</td>
<td>+</td>
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<tr>
<td>mtDNA</td>
<td>Tissue-specific depletion</td>
<td>+</td>
<td>–</td>
<td>–</td>
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<tr>
<td></td>
<td>Deletions</td>
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</tr>
</tbody>
</table>

FRDA = Friedreich’s ataxia; y = years; = not detectable; (+) = uncommon, mild; + = mild to moderate; ++ = severe.

a Sensory and motor axonal neuropathy.
b Epilepsy in IOSCA occurs after the first decade.
c The compound heterozygote IOSCA-patients had transient transaminase elevation resembling the liver involvement in Alpers’ syndrome, and patients with IOSCA, MSCAE and Alpers’ syndrome are susceptible to valproate induced liver toxicity.
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References


