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Clinical letter

Retinoencephalopathy with occipital lobe epilepsy in an OPA-1 mutation carrier

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1. Introduction

A 26-year old warehouse employee first presented with subacute, holocephalic headache of moderate intensity, dizziness, and a "red, flickering pixel" in his right visual field, followed by two bilateral tonic-clonic seizures a few days later. The initial clinical examination, EEG, brain MRI and blood work were unremarkable except for rhabdomyolysis (CK ~10.000 U/l; upper limit of normal is 190 U/l), which was considered as complication associated with tonic-clonic seizures. During the following months, the patient suffered from intermittend fluctuating right visual field phosphenes of increasing size and duration which became permanent later on. Three months after the first seizure, EEG revealed left posterior status epilepticus. Levetiracetam, valproate, carbamazepine, dexamethasone, propofol, phenytoin, phenobarbital, midazolam and perampanel were applied without beneficial effects. Extensive testing for infectious, autoimmune and metabolic etiologies remained inconclusive.

Brain MRI following the diagnosis of focal status epilepticus exhibited a cortical and subcortical T2-signal increase without diffusion restriction in the left occipital pole. Subsequencial, contrast enhanced brain MRIs exhibited a further occipital T2-signal increase in the cortex and adjacent white matter with diffusion restriction but without vascular pathology (Fig. 1A). Proton MR spectroscopy yielded a high lactate peak in the affected occipital brain, whereas *N*-acetyl-aspartate (NAA), a usually highly concentrated brain metabolite and neuronal marker which is synthesized in mitochondria from aspartic acid and acetyl-coenzyme A, was drastically reduced (Fig. 1B). ^{18}FDG-PET indicated left occipital hypermetabolism (Fig. 1D). CSF showed elevated lactate (2.35 mmol/l; upper limit of normal is 2.2 mmol/l) and protein (600 mg/l; upper limit of normal is 400 mg/) levels. Ophthalmological examinations showed central and peripheral visual field deficits and a retinitis pigmentosa-like peripheral fundus without macular or papillary involvement. With decreasing central vision, increasing headaches, colorful phosphenes now appearing in the left visual field and optical hallucinations, repeated brain MRIs showed progressive left occipital atrophy and right occipital disease activity (Fig. 1C). Open skeletal muscle biopsy from vastus lateralis muscle including histochemical examinations showed unspecific results without signs of a mitochondrial dysfunction or mitochondrial proliferation. Molecular genetic testing of skeletal muscle mitochondrial DNA did not show multiple

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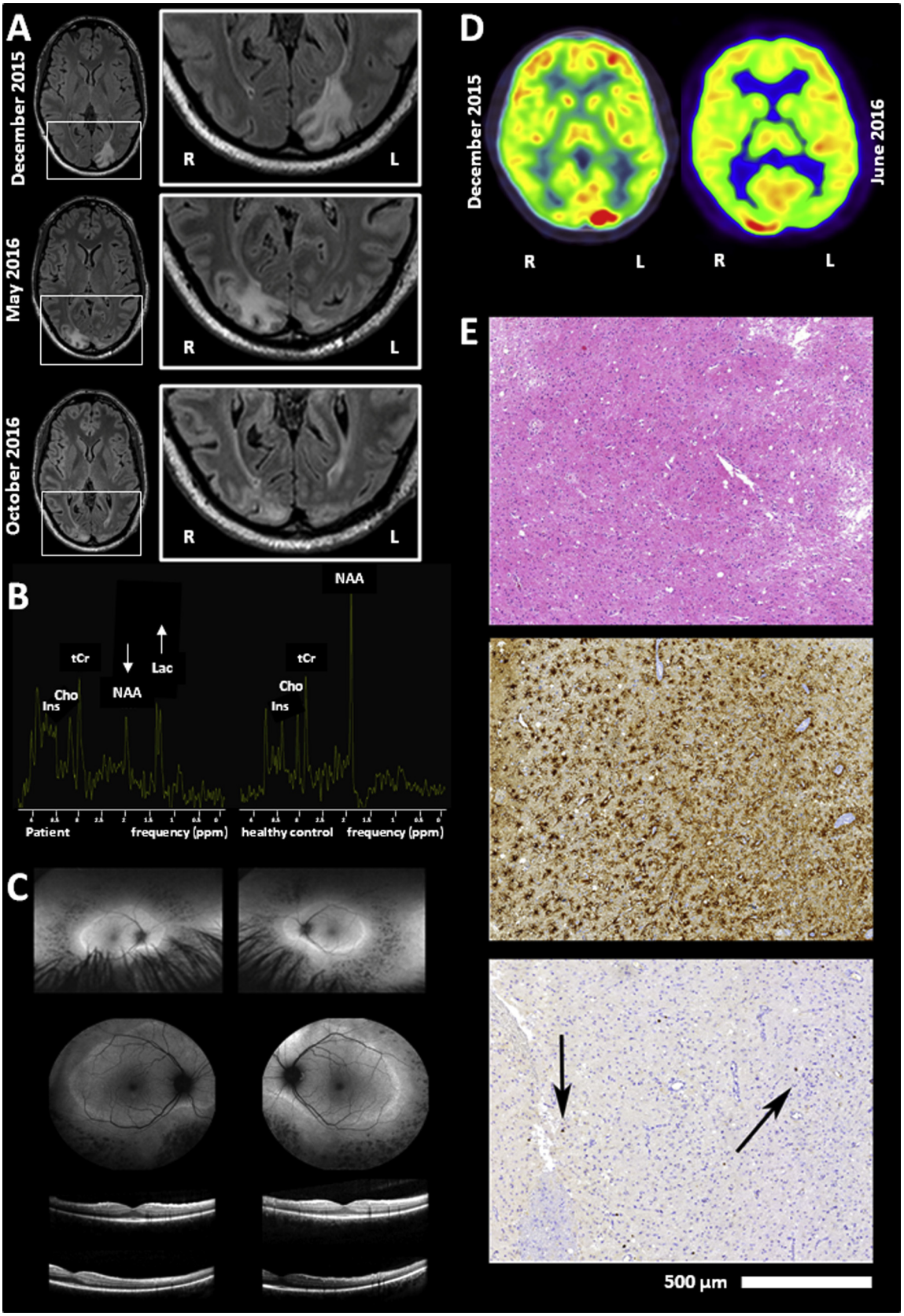

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Fig. 1. shows a synopsis of the patients clinical findings. (A) shows the occipital lesions with focal cerebral edema and gliosis on brain MRI in FLAIR sequences at three time points (from top to bottom: december 2015, may 2016 and october 2016). (B) the proton MR spectrum derived from the hyperintense, right occipital lesion shows a high lactate and drastically reduced NAA signal. (C) shows the eye findings with a peripheral salt and pepper fundus reminiscent of retinitis pigmentosa with normal macula and papilla on ocular coherence tomography. (D) FDG-PET-image shows focal hypermetabolism corresponding to the areas with cerebral edema in Fig. 1A in the early disease course (left, december 2015) and in the later disease course (right, june 2016). (D) shows the biopsied brain tissue. On the hematoxilin & eosin stained paraffin section (top), brain tissue with slightly increased cellularity becomes visible. Importantly, substantial inflammatory infiltrates are absent, thereby not supporting the differential diagnosis of an acute autoimmune pathogenesis of the symptoms in the patient. Immunohistochemistry with antibodies against glial fibrillary acidic protein explains the increased cellularity (middle). A dense reactive cellular astrogliosis is present. Although this observation is not entirely specific, it is well compatible with a metabolic / mitochondrial dysfunction-mediated pathology pattern. Only very sparse CD8-positive T-lymphocytes are present in this brain tissue sample (bottom, black arrows). Respective alterations can often be observed in tissue specimens of chronic epileptic foci. The extent of lymphocytic infiltrates was much too low to represent a neuropathological substrate of acute inflammatory changes (white bar graph in all figures corresponds to 500 µm).

Table 1
Mitochondrial enzyme pattern in the patients fibroblasts.

Parameter	controls (n = 5)	Patient
Citrate synthase (mU/mg protein)	164 ± 82	100
Complex I (mU/mg protein)	26.5 ± 12.2	19.8
Complex I / Citrate synthase	0.17 ± 0.02	0.2
Cytochrome c oxidase (mU/mg protein)	204 ± 125	53
Cytochrome c oxidase / Citrate synthase	1.24 ± 0.76	0.53
Endogeneous respiration (nmol O_2/min/mg)	2.3 ± 0.9	1.8 ± 0.8
Glutamate + malate + ADP (nmol O_2/min/mg)	7.5 ± 1.6	5.9 ± 0.6**
Glutamate + malate + pyruvate + ADP (nmol O_2/min/mg)	8.4 ± 0.3	6.8 ± 0.1*
succinate + rotenone + ADP (nmol O_2/min/mg)	9.7 ± 0.3	8.3 ± 0.4*

** $p < 0.01$.
* $p < 0.05$ (T-test).

mitochondrial DNA deletions and no decrease in mtDNA copy number. Brain biopsy was finally initiated and revealed dense, reactive cellular astrogliosis without major inflammatory infiltrates (Fig. 1E). Although not entirely specific, this observation was deemed compatible with metabolic dysfunction. MERRF, MELAS and POLG-associated diseases were excluded by genetic testing, including mitochondrial whole genome sequencing.

Whole exome sequencing revealed a novel, heterozygous missense variant of the OPA-1-gene c.796 G > A; p.Asp266Asn in exon 8. In silico analysis with four methods (CADD, Polyphen 2, MutationTaster, SIFT) predicted a loss of function effect due to the high conservation of the amino acid at this site. We detected this mutation in the patient's mother who had a normal brain MRI and opthalmological examination and is thus considered to be an asymptomatic carrier. The patient`s brother and father do not carry the mutation. One maternal, fifth degree great-uncle with epilepsy of unknown cause was contacted. He had no visual symptoms, a normal brain MRI and also did not carry the OPA-1 sequence variant.

For further functional assessment of the detected OPA-1 sequence variant, we analyzed the mitochondrial enzyme pattern and the mitochondrial respiration rates of the patient's fibroblasts and compared them to 5 healthy controls. The results are presented in Table 1 and show a clear effect on cytochrome c oxidase activity in the patient`s fibroblasts. This is not only detectable from the enzyme pattern but also visible from the significantly reduced maximal respiration rates of digitonin-permeabilised fibroblasts with glutamate + malate, glutamate + malate + pyruvate and succinate + rotenone as respiratory substrates, which is similar to the findings in other OPA-1 mutations [1].

The patient received supplementary, oral coenzyme Q10, riboflavin, α-lipoic acid and a modified Atkins diet. The disease progression ceased but severe visual field defects persisted. Anticonvulsive drugs were reduced to a combination of levetiracetam and lamotrigine. The diet was stopped by the patient after 6 months but the supplements were continued. At the last follow-up 36 months after onset of the disease, he has suffered no relapse of focal status epilepticus, but continued to experience frequent visual auras and infrequent bilateral tonic clonic seizures at intervals of at least several months.

2. Discussion

The OPA-1 gene encodes a mitochondrial dynamin like GTPase of the inner mitochondrial membrane, which is an essential protein for mitochondrial dynamics and fusion processes as well as for oxidative phosphorylation and mitochondrial DNA maintenance. Pathogenic OPA-1 mutations can lead to autosomal dominant optical atrophy. The "OPA-1 plus" phenotype however may exhibit a plethora of additional neurological features including external ophthalmoplegia. Two patients with “OPA-1 plus” features comprising seizures and migraine were recently reported [2]. The present case may broaden the spectrum of OPA-1 mutation-associated diseases: our patient did not present with optic atrophy but a retinitis-pigmentosa-like phenotype along with highly localized occipital lobe epileptic activity.

The genetic data are not sufficient to prove that the mutation is causative. Several facts, however, support this hypothesis:

1) Primary visual system involvement is frequently present in mitochondrial diseases [3].
2) Increased glucose uptake on ^{18}FDG-PET was similar to acute lesions in MELAS [4], representing a local energy crisis with increased, compensatory glycolysis.
3) Elevated lactate and decreased NAA levels in brain tissue and elevated CSF lactate are in agreement with dysfunction of mitochondrial oxidative phosphorylation.
4) While retinitis pigmentosa is not a specific symptom for a mitochondrial disease, it does coincide frequently with mitochondrial syndromes such as neuropathy, ataxia, and retinitis pigmentosa (NARP) and Kearns-Sayre syndrome.

In summary, we encountered the unusual combination of retinal and occipital lobe anomalies with occipital lobe seizures that we termed retinoencephalopathy. Interdisciplinary cooperation between several basic science and clinical departments finally identified the most likely cause of this disorder: A mitochondrial dysfunction due to an OPA-1 mutation.

Conflicts of interest

None

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