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Presentation of adult mitochondrial epilepsy

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ABSTRACT

Purpose: Mitochondrial disorders (MIDs) frequently manifest phenotypically as epilepsy (mitochondrial epilepsy). Mitochondrial epilepsy occurs in early-onset as well as late-onset syndromic and non-syndromic MIDs. We were interested in the types of epilepsy, the prevalence of mitochondrial epilepsy, the type and effectiveness of treatment, and in the outcome of adult MID patients with epilepsy.
Methods: We retrospectively evaluated adult patients with syndromic or non-syndromic MIDs and epilepsy. MIDs were classified according to the modified Walker criteria as definite, probable, and possible.
Results: Epilepsy in adult patients with a MID was classified as "structural/metabolic" in two-thirds of the cases and as "genetic" in one-third of the cases. Although all types of seizures may occur in mitochondrial epilepsy, adult patients most frequently presented with generalised tonic–clonic seizures, partial seizures, convulsive status epilepticus, or non-convulsive status epilepticus. Cerebral imaging was normal in one-third of the patients. Two-thirds of the adult patients with mitochondrial epilepsy who took antiepileptic drugs received monotherapy, one-third combination treatment. The antiepileptic drugs most frequently administered included levetiracetam, lamotrigine, valproic acid, and gabapentin. Antiepileptic drugs were usually well tolerated and the outcome favourable.
Conclusions: Adult mitochondrial epilepsy appears to be less frequent than previously believed but the prevalence strongly depends on patient selection. Mitochondrial epilepsy is most frequently "structural/metabolic". AEDs recommended for mitochondrial epilepsy include levetiracetam, lamotrigine, gabapentin and lacosamide. The outcome of mitochondrial epilepsy may be more favourable if mitochondrion-toxic AEDs are avoided. Only if non-mitochondrion-toxic AEDs are ineffective, mitochondrion-toxic AEDs may be used.

1. Introduction

Epilepsy is a frequent phenotypic manifestation of syndromic as well as non-syndromic mitochondrial disorders (MIDs).[1] According to the new classification of epilepsies, epilepsy in MIDs may have a genetic or structural/metabolic cause in case of a previous cerebral lesion or dysfunction, or may be of unknown aetiology in case of an undetermined cause.[2] Structural/metabolic epilepsy in MIDs may be due to atherothrombotic or embolic ischaemic stroke, a stroke-like lesion, atrophy, white matter lesions, grey matter lesions, cerebrospinal fluid (CSF)-lactacidosis, cardiac involvement in the MID, endocrinopathy, or due to other disorders, which may cause structural central nervous system (CNS) disease.[3] Epilepsy may be a collateral manifestation of a MID or the dominant feature of the phenotype, such as in mitochondrial encephalopathy, lactacidosis and stroke-like episodes (MELAS)-syndrome, myoclonic epilepsy with ragged-red fibres (MERRF)-syndrome, Leigh-syndrome, myoclonic epilepsy, myopathy and sensory ataxia (MEMSA)-syndrome, also known as spino-cerebellar ataxia with epilepsy (SCAE),

Abbreviations: AED, antiepileptic drug; AHS, Alpers–Huttenlocher-syndrome; CNS, central nervous system; COX, Cytochrome-*c*-oxidase; CPEO, mitochondrial or nuclear chronic progressive external ophthalmoplegia; CSF, cerebro-spinal fluid; EMP, enecephalomyopathy; EP, encephalopathy; EPC, epilepsia partialis continua; IOSCA, infantile-onset spino-cerebellar ataxia-syndrome; KSS, Kearns-Sayre-syndrome; LBSL, leucencephalopathy with brain stem and spinal cord involvement and lactacidosis; LE, leucencephalopathy; LHON, Leber's hereditary optic neuropathy; MDDS, mitochondrial DNA depletion syndrome; MELAS, mitochondrial encephalopathy, lactacidosis and stroke-like episodes-syndrome; MEMSA, myoclonic epilepsy, myopathy and sensory ataxia-syndrome also known as SCAE; MERRF, myoclonic epilepsy with ragged-red fibres-syndrome; LS, Leigh-syndrome; MID, mitochondrial disorder; MIDD, maternally-inherited diabetes and deafness; MILS, maternally-inherited Leigh-syndrome; MIRAS, mitochondrial recessive ataxia syndrome; NARP, neuropathy, ataxia and retinitis pigmentosa; SCAE, spino-cerebellar ataxia with epilepsy; SDH, succinate-dehydrogenase; SUDEP, sudden unexplained death in epilepsy; TCS, tonic–clonic seizure.

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mitochondrial recessive ataxia syndrome (MIRAS), sensory ataxia with neuropathy, dysarthria and ophthalmoparesis (SANDO)-syndrome, or Alpers–Huttenlocher-syndrome (AHS).[3] Little is known about the predominant types and frequency of seizures, treatment and outcome of epilepsy in adult patients with a MID. The present study was therefore designed to describe: (1) which types of epilepsy occur in adult MIDs, (2) what the prevalence of definite, probable or possible mitochondrial epilepsy is in adults, (3) what the most effective treatment is, and (4) what outcome can be most likely expected in these patient groups.

2. Patients and methods

Retrospectively evaluated were patients with syndromic or non-syndromic MIDs and epilepsy, who attended in- or outpatient units of the Krankenanstalt Rudolfstiftung. MIDs were classified according to the modified Walker criteria as definite, probable, and possible.[4] A MID was classified as "definite" if the clinical presentation was indicative of a MID and if there was biochemical (deficiency of complex I, II, or IV of the respiratory chain) or genetic evidence of a mitochondrial defect. A MID was classified as "probable" if the clinical presentation was indicative of a MID and if immuno-histological investigations on muscle biopsy showed COX-negative fibres, ragged-red-fibres, SDH-hyper-reactive fibres, or abnormally shaped or structured mitochondria with or without paracristalline inclusions or glycogen or fat depositions on electron microscopy.[4] A MID was classified as "possible" if the clinical presentation suggested a MID (Table 1) and if instrumental investigations other than a muscle biopsy were indicative of a MID (Table 2).[4] The clinical presentation was considered "suggestive" of a MID if at least 3 of the clinical findings listed in Table 1 were present and if additionally at least 3 instrumental investigations listed in Table 2 were present or if <3 clinical abnormalities and >10 abnormalities on instrumental investigations were found in a single patient.

Included were all patients in whom seizures had occurred previously without requiring antiepileptic drug (AED) treatment at the time of the consultation and those who were taking AED treatment at the time of attendance or had experienced seizures during the last year prior to the consultation. Epilepsy was classified according to its aetiology following the classification of the International League against Epilepsy (ILAE) 2010[2] as genetic or presumed genetic, as structural or metabolic, or unknown. Seizure types were classified as generalised or focal.[2] Epilepsy in MIDs with stroke-like episodes was classified as genetic but not as structural/metabolic since the stroke-like lesion was not regarded as prerequisite for the development of seizures.

Table 1
History, symptoms and signs suggestive of a MID.[1]

PNS	
	Double vision, ptosis, ophthalmoparesis, dropped head, camptocormia, cervical spine syndrome, limb weakness, muscular respiratory insufficiency, exercise intolerance, fatigue, easy fatigability, sore muscles, myalgia, muscle cramps, sensory disturbances, sensory ataxia, muscle rupture
CNS	
	Disorientation, confusion, autism, psychosis, lethargy, cognitive decline, dementia, seizures, stroke-like episode, ischaemic stroke, hypersomnia, migraine, migraine-like headache, cluster headache, cerebellar ataxia, movement disorder, transverse syndrome
Eyes	
	Visual impairment, blurred vision, visual field defects, painful bulbs
Ear	
	Hypoacusis, acute hearing loss, tinnitus
Endocrine organs	
	Short stature, sicca-syndrome, hyperhidrosis, impotence, hypogonadism, adynamia
Heart	
	Palpitations, orthopnoe, exertional dyspnoea, leg oedema, neck vein distension, recurrent syncopes, sudden cardiac death
Gastrointestinal	
	Dysphagia, vomiting, diarrhoea, obstipation, jaundice, colics, pancreatitis
Kidneys	
	Colics from nephrolithiasis
Skeleton	
	Scoliosis, arthralgia, dysmorphism

Table 2
Unexplained instrumental findings other than a muscle biopsy or genetic testing indicative of a MID.[1]

Cerebral imaging	
	Basal ganglia calcification, focal cerebral atrophy, white matter lesions, stroke-like lesion, optic atrophy, pituitary adenoma, empty sella
PNS	
	Polyneuropathy, motor neuron disease, myopathy
Eyes	
	Pigmentary retinopathy, cataract, glaucoma, prolonged visually evoked potentials
Ears	
	Hypoacusis on audiometry
Serum/CSF tests	
	Elevated serum/CSF lactate, elevated CSF protein, pleocytosis, recurrent CK-elevation, elevated liver function parameters, elevated amylase, renal insufficiency, hyperlipidemia, hyperuricemia
Blood cells	
	Anaemia, thrombopenia, thrombocytosis, leucopenia, eosinophilia
Heart	
	Hypertrophic cardiomyopathy, dilative cardiomyopathy, left ventricular hypertrabeculation (noncompaction), Takotsubo syndrome, arrhythmias
Kidneys	
	Kidney cysts, nephrolithiasis, renal failure
Guts	
	Parotitis, hepatopathy, liver cysts, pancreatitis, pancreatic cysts. diverticulosis, "nonspecific" colitis
Endocrinium	
	Osteoporosis, hypopituitarism, hypocorticism, diabetes, hypoaldosteronism, hypothyroidism, hyperthyroidism, hypogonadism
Vessels	
	Atherosclerosis, arterial stenosis, occlusion, aneurysm, ectasia, dissection, or rupture
Skin	
	Madarosis, psoriasis, lipomatosis

3. Results

Altogether, 444 patients were classified as MID during the observation period of 4 years, 15 as definite, 54 as probable and 375 as possible MID (Table 3). Insufficient or inconclusive data concerning epilepsy were available in 3 patients (Table 3). Among the remaining 441 patients, epilepsy was associated with a MID in 60 patients: in 3 cases MID was categorised as definite, in 12 as probable, and in 45 as possible (Table 3). Among the 3 patients with definite MID and epilepsy one presented with syndromic MID (MELAS-syndrome (respiratory chain complex defect, >2% ragged-red fibres, >2% COX-negative fibres)) and two with non-syndromic MIDs. One of the patients with definite non-syndromic MID had a multisystem disease with multiple respiratory chain complex deficiencies and the second patient epilepsy and cardiomyopathy with complex-I defect, >2% ragged-red fibres, >2% COX-negative fibres, and para-cristalline inclusions on electron microscopy. The number of abnormalities listed in Tables 1 and 2 found in the 45 possible MIDs are presented in Table 4.

Among the 60 patients with epilepsy 38 were female and 22 male. Mean age was 67.2 years (range: 35–90 years). None of the patients with probable MIDs and epilepsy fitted into a distinct mitochondrial syndrome. Epilepsy had a structural/metabolic aetiology in 39 cases. It was attributed to previous ischaemic stroke in 14 patients, to chronic alcohol consumption in 8, to cerebral atrophy in 7, to a cerebral tumour in 3, to a head trauma, encephalitis, or hypoxia each in 2, and to superficial siderosis in 1 (Fig. 2). In 21 patients, epilepsy was classified as genetic,