

# Cerebral Manifestations of Mitochondrial Disorders

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**ABSTRACT:** This review aims at summarizing and discussing previous and recent findings concerning the cerebral manifestations of mitochondrial disorders (MIDs). MIDs frequently present as mitochondrial multiorgan disorder syndrome (MIMODS) either already at onset or later in the course. After the muscle, the brain is the organ second most frequently affected in MIMODS. Cerebral manifestations of MIDs are variable and may present with or without a lesion on imaging or functional studies, but there can be imaging/functional lesions without clinical manifestations. The most well-known cerebral manifestations of MIDs include stroke-like episodes, epilepsy, headache, ataxia, movement disorders, hypopituitarism, muscle weakness, psychiatric abnormalities, nystagmus, white and gray matter lesions, atrophy, basal ganglia calcification, and hypometabolism on 2-deoxy-2-[fluorine-18]fluoro-D-glucose positron-emission tomography. For most MIDs, only symptomatic therapy is currently available. Symptomatic treatment should be supplemented by vitamins, cofactors, and antioxidants. In conclusion, cerebral manifestations of MIDs need to be recognized and appropriately managed because they strongly determine the outcome of MID patients.

**RÉSUMÉ:** Manifestations cliniques cérébrales relatives aux troubles mitochondriaux. Cet article vise à résumer et à aborder les conclusions, à la fois antérieures et récentes, relatives aux manifestations cliniques cérébrales des troubles mitochondriaux. De façon générale, ces manifestations sont fréquemment l'expression du syndrome de défaillance multi-viscérale d'origine mitochondriale, que ce soit à ses débuts ou lors de son évolution. Après les muscles, le cerveau est l'organe le plus fréquemment affecté lorsqu'on diagnostique un syndrome de défaillance multi-viscérale. De telles manifestations cliniques cérébrales demeurent variables ; elles peuvent (ou ne pas être) associées à des lésions à la suite d'examens d'imagerie cérébrale ou d'études fonctionnelles. Cela étant, il est possible que de telles lésions n'entraînent aucune manifestation clinique. Parmi les manifestations cliniques cérébrales des troubles mitochondriaux les plus répandues, on peut inclure des pseudo-AVC (*stroke-like episodes*), l'épilepsie, des maux de tête, l'ataxie, des troubles du mouvement, l'hypopituitarisme, de la faiblesse musculaire, des problèmes psychiatriques, le nystagmus, des lésions de la substance blanche ou de la substance grise, l'atrophie, la calcification des noyaux gris centraux et l'hypo-métabolisme de la molécule 2-désoxy-2-[<sup>18</sup>F]fluoro-D-glucose détecté lors d'un examen de tomographie par émission de positrons. Pour la plupart de ces manifestations, seul un traitement symptomatique est offert à l'heure actuelle. Un tel traitement devrait être complété par la prise de vitamines, de cofacteurs et d'antioxydants. En conclusion, les manifestations cliniques cérébrales des troubles mitochondriaux doivent être détectées et soignées de façon appropriée car elles ont une grande incidence sur l'évolution de l'état de santé des patients.

**Key words:** brain, cerebral MRI, mitochondrial, oxidative phosphorylation, respiratory chain

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## INTRODUCTION

Mitochondrial disorders (MIDs) are usually multisystem diseases (mitochondrial multiorgan disorder syndrome [MIMODS]), either already at onset or with progression of the disease.<sup>1</sup> One of the organs most frequently involved in MIDs is the brain.<sup>2</sup> Cerebral manifestations in MIDs are variable and may be classified as pure clinical without abnormalities on imaging or functional studies, as clinical with functional or imaging abnormalities, or as functional or imaging abnormalities without appropriate clinical manifestations (Table 1).<sup>2</sup> This review aims at summarizing and discussing recent findings and future perspectives concerning the clinical presentation, pathophysiology, diagnosis, treatment, and outcome of cerebral disease in MIDs.

## CLASSIFICATION

Cerebral abnormalities in MIDs may not only be classified as pure clinical (e.g. headache) or as clinical with abnormalities on functional or imaging studies (e.g. stroke-like episode [SLE]) but,

depending on the affected tissue, also as vascular, astrocytic, or neuronal. Cerebral manifestations of MIDs may be permanent (e.g. dementia) or transient (e.g. seizure, SLE, headache) and may be a direct consequence of the metabolic defect (e.g. SLE) or secondary resulting from involvement of other organs (e.g. stroke from atrial fibrillation, bleeding from hypertension). Central nervous system (CNS) abnormalities of MIDs may be also categorized as treatable (e.g. epilepsy) or inaccessible to treatment (e.g. basal ganglia calcification, atrophy). Additionally, a CNS abnormality may go along with or without other CNS abnormalities attributable to the MID. Furthermore, cerebral abnormalities in MIDs may or may not be accompanied by manifestations in other organs (MIMODS). CNS involvement in MIDs may be also categorized according to

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**Table 1: Classification of CNS abnormalities in MIDs according to the predominant presentation either on clinical examination or on imaging/functional studies**

CNS manifestation	Imaging/FS*	Clinical only	Both
SLE	x		x
Epilepsy		x	x
Headache		x	x
Ataxia		x	x
Movement disorder		x	x
HHAA		x	x
Muscle weakness		x	x
Psychiatric abnormality		x	x
Nystagmus		x	x
White matter lesions	x		x
Gray matter lesions	x		x
Atrophy	x		x
Basal ganglia calcification	x		x
Hypometabolism on FDG-PET	x		x
Optic atrophy		x	x
Central sleep apnea syndrome	x		x

\*Instrumental investigations are inevitable for diagnosing stroke-like episodes (SLEs), gray matter lesions, white matter lesions (WMLs), cerebral atrophy, basal ganglia calcification, hypometabolism, and sleep apnea syndrome.

FS = functional studies, HHAA = hypothalamic-hypophysial-adrenal axis.

the affected anatomical structure (cortex, subcortical, white matter, basal ganglia, thalamus, midbrain, pons, cerebellum, medulla, or spinal cord) or according to the onset of the clinical manifestations as early or late onset. Finally, cerebral lesions can be delineated from spinal cord lesions and CNS lesions resulting from respiratory-chain defects can be delineated from CNS lesions from nonrespiratory chain mitochondrial defects.

### CNS MANIFESTATIONS OF MIDs

There are several clinical CNS abnormalities with or without concomitant morphological/functional abnormalities and several morphological and functional abnormalities with or without clinical manifestations, which have been identified as manifestations of specific and nonspecific MIDs (nsMIDs) (Table 1). These include SLEs, epilepsy, headache, ataxia, movement disorders, nystagmus, muscle weakness, insufficiency of the hypothalamic-hypopituitary-adrenal axis, muscle weakness, psychiatric abnormalities, nystagmus, white matter lesions (WMLs), gray matter lesions, atrophy, basal ganglia calcification, and hypometabolism on 2-deoxy-2-[fluorine-18]fluoro-D-glucose positron-emission tomography (FDG-PET) (Table 1).

### SLEs

SLEs are a typical phenotypic feature of mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome, with which they occur in the majority of

the patients. However, SLEs have been also reported in patients with myoclonus epilepsy with ragged-red fibers (MERRF) syndrome,<sup>4</sup> Kearns-Sayre syndrome (KSS),<sup>5</sup> Saguenay-Lac-St. Jean cytochrome oxidase deficiency,<sup>6</sup> Leigh syndrome,<sup>7</sup> and coenzyme-Q deficiency resulting from *ADCK3* mutations.<sup>8</sup> Additionally, SLEs have been reported in nonmitochondrial conditions, such as X-linked hereditary motor and sensory neuropathy (HMSN1),<sup>9</sup> neurobrucellosis,<sup>10</sup> cerebral amyloid angiopathy,<sup>11</sup> or sarcoidosis.<sup>12</sup> Clinical presentation of SLEs can be heterogeneous.<sup>3</sup> The most frequent symptom of an SLE is cortical blindness.<sup>3</sup> Other clinical manifestations include psychiatric disorders,<sup>13</sup> epilepsy,<sup>14</sup> headache,<sup>15</sup> hemiparesis,<sup>16</sup> and various types of aphasia.<sup>17</sup> More rarely, visual agnosia, prosopagnosia, cortical deafness, auditory agnosia (from the mutation m.10197G > A), topographical disorientation, disinhibition, agitation, euphoria, anxiety, impaired face recognition, prolonged visual aura, hemianopia or quadrantanopia, or hemispatial neglect have been reported.<sup>3,17,18</sup>

The morphological correlate of an SLE on cerebral imaging is the stroke-like lesion (SLL). Depending on the interval after onset, an acute or chronic stage of an SLL can be delineated. The acute stage of an SLL on magnetic resonance imaging (MRI) is characterized by hyperintensity on T2-w/fluid-attenuated inversion recovery images, hyperintensity on diffusion weighted imaging (DWIs), and hyperintensity on apparent diffusion coefficient (ADC) maps (Figure 1). Occasionally, areas with cytotoxic edema within the SLL may be found. Blood flow is increased on perfusion weighted imaging in the acute stage. Magnetic resonance spectroscopy may show a lactate peak and a reduced N-acetyl-aspartate/creatine ratio indicating neuronal death (Table 2).<sup>19,20</sup> A lactate peak is regarded as abnormal only if the N-acetyl-aspartate/choline ratio is normal. In a study of 13 patients with, altogether, 44 SLLs, DWI showed hyperintensity in 37 and isointensity in seven cases.<sup>21</sup> On ADC, 16 were hyperintense, 16 hypointense, and 15 isointense.<sup>21</sup> The chronic stage of SLLs is characterized by spreading and later regression of the lesion, hyperintensity, hypointensity, or isointensity on T2,<sup>21</sup> hyperintensity, fainting or disappearance on DWI, hypointensity or isointensity on ADC, and hypoperfusion.<sup>19</sup> Outcomes from SLLs include complete recovery, focal atrophy, laminar cortical necrosis, or a WML.<sup>21,22</sup> Besides SLEs, patients with MIDs may experience ordinary ischemic strokes or transitory ischemic attacks secondary to cardiac involvement in the MID.<sup>23</sup> SLEs are frequently accessible to the nitric oxide precursors L-arginine (500 mg/kg/d), citrulline, or succinate. Supportive measures include a ketogenic diet<sup>24</sup> and symptomatic treatment of the various clinical manifestations of an SLE.<sup>25</sup>

### Epilepsy

Mitochondrial epilepsy is a common feature of specific and nsMIDs. Epilepsy may be the dominant feature (e.g. MERRF) or nondominant feature (e.g. Leber hereditary optic neuropathy (LHON)) of the phenotype. All types of seizures may occur with mitochondrial epilepsy, but focal seizures appear more frequent than generalized seizures. However, no systematic studies on this matter have been carried out. According to a literature review, focal seizures with secondary generalization were more prevalent than primary generalized seizures in pediatric MIDs, which are

**Table 2: Specific and nonspecific MIDs with CNS involvement and location of the predominant genetic defect**

MID	CNS manifestation	mtDNA	nDNA
MELAS	SLE, E, H, A, MD, HH, P, N, W, G, AT, C, HM	x	
MERRF	SLE, E, H, A, MD, HH, P, G, AT	x	
KSS	SLE, E, A, HH, P, WML, AT, C	x	
LRPPRC	SLE		x
LS	SLE, E, H, A, MD, W, P, WML, G, C, HM	x	x
CoQ-def.	SLE, W		x
MEMSA	E		x
MIRAS	E, H, A		x
IOSCA	E, P		x
LBSL	E, WML		x
AHD	E, P		x
LHON	E, H, MD, HH, P, N, WML, AT	x	
NARP	E, A, P, W	x	
SANDO	E, A		x
CPEO	H, MD, P, AT	x	
CVS	H		x
MDS	H, A, N		x
nsMIDs	H, A, HH, W, P, N, WML, AT, C	x	x
XLSA	A		x
PDH	A, AT		x
MSL	A		x?
DCMA	A		x
PCH	A, WML, AT		x
MNGIE	P, WML, G, HM		x

? = uncertain, A = ataxia, AT = cerebral atrophy, C = basal ganglia calcification, CoQ-def = coenzyme Q deficiency, DCMA = dilated cardiomyopathy with ataxia, E = epilepsy, G = gray matter lesions, H = headache, HH = hypothalamic-hypophysial axis, HM = hypometabolism, IOSCA = infantile onset spinocerebellar ataxia, LBSL = leukoencephalopathy, brainstem and spinal cord lesions, and lactic acidosis, MD = movement disorder, MEMSA = myoclonic epilepsy myopathy sensory ataxia, MSL = multiple systemic lipomatosis, N = nystagmus, P = psychiatric abnormalities, SANDO = sensory ataxic neuropathy, dysarthria, and ophthalmoparesis, W = muscle weakness or hypotonia, WML = white matter lesions

more frequently the result of nuclear DNA than mitochondrial DNA (mtDNA) mutations.<sup>26</sup> In adult MIDs, which are more frequently from mtDNA than nuclear DNA mutations, generalized seizures are more prevalent than focal seizures.<sup>26</sup> A common type of epilepsy in MIDs is myoclonic epilepsy. Among the specific MIDs, mitochondrial epilepsy with early onset occurs in MELAS, MERRF, KSS, Leigh syndrome, myoclonic epilepsy myopathy sensory ataxia, mitochondrial recessive ataxia syndrome (MIRAS), infantile onset spinocerebellar ataxia (IOSCA), leukoencephalopathy, brainstem and spinal cord lesions, and lactic acidosis, and Alpers-Huttenlocher syndrome.<sup>26</sup> Mitochondrial epilepsy with adult onset has been reported in MELAS, LHON, neuropathy

ataxia and retinitis pigmentosa (NARP), and sensory ataxic neuropathy, dysarthria, and ophthalmoparesis.<sup>26</sup> In a study of seven MELAS patients, seizures usually occurred during the acute phase of an SLE and included epilepsy partialis continua, hemiconvulsive status epilepticus, nonconvulsive status, and occipital status epilepticus.<sup>27</sup> Among pediatric patients, infantile spasms, refractory or recurrent status epilepticus, epilepsy partialis continua, and myoclonic epilepsy were the most prevalent seizure types.<sup>28</sup> In a retrospective study of 109 pediatric and adult MID patients undergoing electroencephalography, 85% had epileptiform discharges, including multifocal discharges (41%), focal discharges (39%), and generalized discharges (39%).<sup>29</sup> The most common types of seizures were complex partial (37%) and generalized tonic-clonic (39%).<sup>29</sup> Among those with seizures (55%), 28% were intractable to treatment.<sup>29</sup> Patients with Leigh syndrome most commonly had focal or generalized seizures (11% in both) and patients with MELAS most commonly had generalized seizures (33%).<sup>29</sup> NARP may be associated with catastrophic epilepsy.<sup>30</sup> Intractable seizures with epileptic encephalopathy have been also reported in patients carrying *CARS2* mutations associated with combined respiratory chain deficiency of complexes I, III, and IV (Table 3).<sup>31</sup>

Treatment of mitochondrial epilepsy mainly relies on anti-epileptic drugs (AEDs). Additional measures include epilepsy surgery, diets, vagal nerve stimulation, and supportive agents.<sup>32</sup> Treatment should start with AEDs with a low mitochondrion-toxic potential, such as levetiracetam, lamotrigine, gabapentin, or zonisamide. Only when these agents are ineffective or accompanied by severe side effects should AEDs with high mitochondrion-toxic potential, such as valproic acid, carbamazepine, phenytoin, or phenobarbital, be tried.<sup>32</sup> Valproic acid seems to have one of the highest mitochondrion-toxic potentials, which is why it should be avoided particularly in patients carrying *POLG1* mutations or in patients with MERRF. In all patients with mitochondrial epilepsy, a ketogenic diet should be considered as a supportive measure. In some cases, a ketogenic diet may be the only effective treatment of mitochondrial epilepsy.<sup>33</sup> Whether the application of vitamins, cofactors, or antioxidants has an additional beneficial effect on mitochondrial epilepsy has not been systematically investigated.<sup>32</sup> In single cases with MELAS syndrome, L-arginine has been shown to be beneficial not only for SLEs, but also for seizures, including status epilepticus.<sup>34</sup>

## Headache

Headache as a feature of a MID manifests as migraine-like headache, cluster headache, nonclassified headache, or tension headache. Headache may be the dominant feature of a MID or only an ancillary feature of the phenotype. Headache may manifest as a pure manifestation of a MID or may be part of a MIMODS. For example, migraine-like headache may be an isolated manifestation of a MID or may occur together with MELAS, MERRF, chronic progressive external ophthalmoplegia (CPEO), LHON, Leigh syndrome, MIRAS, cyclic vomiting syndrome, mitochondrial depletion syndrome (MDS), or nsMIDs. Nonclassified headache has been reported in patients carrying *POLG1* mutations.<sup>35</sup> If headache during an SLE is resistant to L-arginine, midazolam may be effective alternatively.<sup>15</sup> Unfortunately, headache is only insufficiently described in most MID cases. Up to 58% of the patients

**Table 3: Respiratory chain defects in MIDs with CNS involvement**

	CI	CII	CIII	CIV	CV
AHS	NR	NR	NR	x	NR
CPEO	x	NR	x	x	x
IOSCA	NR	NR	NR	NR	NR
KSS	NR	NR	NR	x	NR
LBSL	NR	NR	NR	NR	NR
LHON	x	NR	NR	x	NR
MDS	x	x	x	x	x
MELAS	x	NR	x	x	x
MERRF	x	NR	x	x	NR
MIRAS	x	NR	NR	x	NR
MNGIE	NR	NR	NR	x	NR
MSL	NR	NR	NR	NR	NR
NARP	NR	NR	NR	NR	NR
PCH	NR	NR	NR	NR	NR
SANDO	NR	NR	NR	IV	NR
XLSA	NR	NR	NR	NR	NR
MIMODS	x	NR	x	x	NR

AHS = Alpers-Huttenlocher syndrome, NR = not reported.

carrying the m.3243A > G mutation develop migraine.<sup>36</sup> Migraine may be also part of the clinical presentation of an SLE.<sup>13</sup> The pathophysiology of migraine-like headache is poorly understood, but there are indications that it is a vascular pathology, resulting in initial hyperperfusion, which results from activation of the calcitonin-related protein or from enhanced influx of calcium into mitochondria resulting in increased oxidative stress.<sup>37</sup> Whether lactic acidosis plays a role in the development of headache in MID patients remains speculative. Only few MIDs with cluster headache have been reported.<sup>38</sup> Treatment of headache in MIDs is the same as in non-MID patients. Migraine and migraine-like headache in MIDs may respond to nonsteroidal antirheumatic drugs, vitamin supplementation, and triptans.<sup>39</sup> Additionally, migraine may be accessible to ketogenic diet in single patients (personal communications with patients). Headache during SLEs may respond to L-arginine or midazolam.<sup>15</sup>

### Ataxia

Ataxia is a frequent clinical manifestation of MIDs with CNS involvement. Ataxia in MIDs may dominate the phenotype or may be only an ancillary phenotypic feature. Ataxia may or may not be associated with a cerebellar or basal ganglia lesion. MIDs in which ataxia may dominate the phenotype include X-linked sideroblastic anemia with ataxia (XLSA), pyruvate-dehydrogenase (PDH) deficiency, NARP, MIRAS, and some nsMIDs. XLSA is characterized by early-onset sideroblastic anemia and cerebellar ataxia.<sup>40</sup> Ataxia in XLSA is usually non-progressive, but a few cases with mild progression after the fifth decade have been reported. Ataxia predominantly manifests as gait or trunk ataxia, which may be accompanied by dysdiadochokinesia, dysmetria, dysarthria, nystagmus, hypometric

saccades, strabism, or tremor.<sup>2</sup> Only some patients additionally develop lower-limb spasticity.<sup>41</sup> Occasionally, female carriers of the X-linked forms manifest clinically.<sup>42</sup> XLSA is genetically heterogeneous and may be due to mutations in the *ALAS2*, *TRTN1*, or *ABCB7* genes. PDH deficiency is a rare, nonrespiratory chain associated MID resulting from mutations in the *PDHA*, *PDHB*, *PDHC*, and *PDHD* genes, which encode the four subunits of the PDH complex. PDH deficiency manifests with a wide range of abnormalities, from isolated lactic acidosis to severe Leigh syndrome.<sup>43</sup> Some cases may present with isolated intermittent ataxia.<sup>44</sup> Rarely, chromosomal defects have been reported as causative.<sup>45</sup> NARP is a specific MID resulting from mutations in the *ATP6* gene. It is clinically characterized by muscle weakness, ataxia, and retinitis pigmentosa. Additional phenotypic features may be learning difficulties since childhood, deafness, muscle weakness, and myoclonus. The NARP mutation m.8993T > C may also cause adult-onset myoclonus ataxia.<sup>46</sup> MIRAS is a mitochondrial syndrome resulting from *POLG1* mutations (c.1399G > A and 2243G > C) with early-onset ataxia. Ataxia occurs as a collateral feature in MELAS, MERRF, KSS, Leigh syndrome, multiple systemic lipomatosis, MDS, sensory ataxic neuropathy, dysarthria, dilated cardiomyopathy with ataxia, pontocerebellar hypoplasia (PCH),<sup>47</sup> sensory ataxic neuropathy, dysarthria, and ophthalmoparesis, and some nsMIDs. In a study of 126 MID patients with cerebellar ataxia, 24 had pure ataxia and 102 ataxia with other MID manifestations.<sup>48</sup> Among patients with idiopathic cerebellar ataxia, 28% had a MID.<sup>48</sup> Ataxia in MIDs is hardly accessible to treatment, which is why only supportive measures and administration of vitamins, coenzymes, or antioxidants can be offered.

### Movement Disorders

Movement disorders are a group of neurodegenerative diseases characterized by involuntary movements of the eyes, head, trunk, or limbs, at rest or during movements. Movement disorders are characterized by either paucity or excess of involuntary/asymptomatic or voluntary movements unrelated to weakness or spasticity.<sup>49</sup> Two main groups of movement disorders are delineated: the akinetic-rigid syndromes (e.g. Parkinson syndrome) and the hyperkinetic-dyskinetic syndromes (e.g. restless leg syndrome, tremor).<sup>49</sup> Any of these types of movement disorders have been occasionally described in single cases or small case series of patients with specific or nsMIDs,<sup>50</sup> and there is increasing evidence that movement disorders can be a major part of the phenotypic spectrum of MIDs.<sup>51</sup> However, there are only a few retrospective studies commenting on movement disorders in a larger group of genetically or biochemically confirmed MIDs available. In a recent retrospective study, 42 patients with a movement disorder were identified among 678 MID patients.<sup>50</sup> Almost two-thirds of the 42 cases were male. Parkinsonism was found in 13 patients and dystonia in 11. The most frequent imaging abnormality among the 42 patients was basal ganglia calcification, which was associated with generalized dystonia or Leigh syndrome.<sup>50</sup> Dystonia was the most common movement disorder among pediatric patients and most commonly associated with mtDNA mutations. Parkinsonism was the most frequent movement disorder among adult MID patients and was most commonly associated with *POLG1* mutations.<sup>50</sup> Parkinson syndrome has been also reported in patients with a deletion of the *cytb* gene,<sup>52</sup> in

MERRF,<sup>53</sup> CPEO from *C10orf2* mutations,<sup>54</sup> in nsMIDs from mutations in the *STXBPI* gene<sup>55</sup> or MPV17,<sup>56</sup> and in MIDs from the m.4296G > A mutation.<sup>57</sup> Dystonia has been most frequently reported in MELAS, where it may be the presenting manifestation,<sup>58</sup> in MERRF in the form of spasmodic dysphonia,<sup>59</sup> in LHON,<sup>60</sup> and in nsMIDs from *SUCLA2* mutations<sup>61</sup> or the m.8332A > G mutation.<sup>62</sup> Some patients with complex-I defect or PDH deficiency may develop exertion-induced dystonia.<sup>63</sup> Paroxysmal exercise-induced dystonia may occur in patients with mitochondrial ECHS1 deficiency. Treatment of movement disorders in MIDs is not different from non-MID movement disorders, but occasionally less effective.<sup>25</sup>

### Hypothalamic-Hypophysial-Adrenal Axis (HHAA)

Involvement of the HHAA may manifest as hypopituitarism or pituitary adenoma. Hypopituitarism may manifest as short stature, hypothyroidism, hypocorticism, hypogonadism, polydipsia, or arterial hypotonia. Hypopituitarism has been reported in MELAS,<sup>64</sup> KSS,<sup>65</sup> or nsMIDs from mutations in the *isoleucyl t-RNA synthetase* gene.<sup>66</sup> Pituitary adenoma has been reported in LHON<sup>67</sup> and some nsMIDs.<sup>68</sup> Supplementation of decreased hormone levels has been tried with a beneficial effect in single cases.<sup>69</sup>

### Muscle Weakness

Weakness of bulbar muscles in MIDs may occasionally be due to affection of the upper motor neuron or involvement of the intracerebral segment of the lower motor neuron. Involvement of the upper motor neuron may go along with muscle weakness and spasticity, exaggerated tendon reflexes, and positive pyramidal signs. Involvement of the intracerebral segment of the lower motor neuron can go along with muscle weakness, muscle hypotonia, and reduced tendon reflexes, such as in Leigh syndrome. There are also cases that present with spasticity but without muscle weakness and also cases with muscle hypotonia but without muscle weakness. If cranial nerves innervating bulbar muscles are affected, dysarthria, dysphagia, and tongue or facial weakness and wasting may ensue. If bulbar involvement is due to an upper motor neuron lesion, the masseter reflex may be exaggerated. Involvement of the bulbar muscles and the limb muscles together with pyramidal signs may give rise to mix up a MID with amyotrophic lateral sclerosis.<sup>1</sup> Spasticity with muscle weakness has been reported in CHCHD10 disorders<sup>70</sup> and complex I deficiency.<sup>71</sup> Spasticity without muscle weakness has been reported in nsMIDs from an *SPG7* mutation.<sup>72</sup> Hypotonia with muscle weakness has been found in nsMIDs from *PMPCA* mutations.<sup>73</sup> Muscle hypotonia without muscle weakness has been observed in coenzyme-Q deficiency<sup>74</sup> and other MIDs (Table 2). Only supportive measures are available to influence muscle weakness, hypotonia, and spasticity.

### Psychiatric Abnormalities

The main psychiatric abnormalities associated with MIDs include cognitive deterioration including dementia, mood disorders, anxiety disorders, and psychosis.<sup>75</sup> More rarely reported are attention deficit hyperactivity disorder in Leigh syndrome,<sup>76</sup> autism spectrum disorders,<sup>77</sup> Münchausen syndrome, and bipolar disorder.<sup>78</sup> Psychiatric disorders in MIDs may go along with or

without neurological abnormalities. This is why isolated psychiatric disease has to be considered as a manifestation of a MID. Cognitive dysfunction has been occasionally reported in MIDs with diffuse cerebral lesions but not in cases with SLEs.<sup>3</sup> Affected domains of cognitive function include abstract reasoning, verbal memory, visual memory, language (naming and fluency), executive or constructive functions, attention, and visuospatial function.<sup>3</sup> Cognitive impairment may be a transient condition if it is due to a complex partial seizure or a permanent or even progressive condition if it is the direct manifestation of the underlying metabolic defect. Cognitive dysfunction has been reported in MELAS,<sup>3</sup> MERRF, NARP,<sup>79</sup> LHON, CPEO, KSS, mitochondrial neurogastrointestinal encephalopathy (MNGIE), Leigh syndrome, and Alpers-Huttenlocher syndrome.<sup>80</sup> Mitochondrial dementia has been recognized in MELAS,<sup>81</sup> MERRF,<sup>82</sup> KSS,<sup>83</sup> CPEO,<sup>84</sup> and nsMIDs due to the m.586G > A mutation in the *tRNA(Phe)* gene.<sup>85</sup> Mood disorders, such as depression, have been observed in MELAS where it may be treatment-resistant,<sup>75,86</sup> MERRF,<sup>87</sup> NARP,<sup>88</sup> CPEO due to *C10orf2* (*twinkle*) mutations,<sup>54,89</sup> *POLG1*-related disorders,<sup>90</sup> and in nsMIDs.<sup>91</sup> An anxiety disorder as a manifestation of a MID has been described in nsMIDs.<sup>91</sup> Psychosis has been reported in MELAS,<sup>86</sup> KSS,<sup>92</sup> *POLG1*-related disorders,<sup>93</sup> infantile onset spinocerebellar ataxia,<sup>94</sup> Leigh syndrome,<sup>95</sup> and nsMIDs.<sup>96</sup> Psychiatric abnormalities particularly occur in patients with MELAS, in which 50% of cases are affected.<sup>75</sup> Psychiatric abnormalities in MELAS other than those described previously include borderline personality disorder,<sup>75</sup> confusional states,<sup>86</sup> logorrhea, disinhibition, agitation, and euphoria.<sup>17</sup> Psychiatric abnormalities may even be the presenting manifestation of MELAS.<sup>75</sup> Psychiatric disorders in MIDs are treated in the same way as in non-MID patients, but there are few data about mitochondrion toxicity of antipsychotic drugs available.<sup>25</sup>

### Nystagmus

Spontaneous, gaze-evoked, or pursuit-paretic nystagmus is an infrequent clinical manifestation of a MID and rarely occurs as an isolated phenotypic feature. Together with other CNS or extra-CNS abnormalities, it has been reported most frequently in Leigh syndrome<sup>97,98</sup> and more rarely in LHON,<sup>99</sup> MELAS,<sup>100</sup> MDS from *DGUOK* deficiency,<sup>101</sup> *POLG1*-related disorders,<sup>102</sup> or in nsMIDs.<sup>103-105</sup> Downbeat nystagmus has been reported in a patient with MELAS syndrome as a result of the *tRNA(Leu)* mutation m.3271T > C.<sup>106</sup> Nystagmus may also be due to vestibular involvement in the MID, which can be differentiated by vestibular testing.<sup>107</sup> Nystagmus has to be further differentiated from epileptic nystagmus.<sup>100</sup> In a retrospective study of 59 patients with genetically confirmed MID, nine (5.3%) presented with nystagmus.<sup>108</sup> There is no specific treatment of nystagmus available, but in some cases it may respond to non-specific therapy with vitamins, cofactors, or antioxidants given as a general supportive treatment in MIDs.<sup>109</sup>

### WMLs

WMLs are the most frequent morphological CNS abnormality of MIDs. They may or may not be accompanied by clinical manifestations, other CNS abnormalities, or non-CNS manifestations. WMLs may coexist with gray matter lesions such as in MNGIE resulting from *TYMP* mutations.<sup>110</sup> The morphology of WMLs in

MIDs is quite variable, which is why they may be easily mixed up with other CNS disorders; other hereditary leukoencephalopathies, leukodystrophies, and multiple sclerosis particularly can be easily mixed up with WMLs in MIDs. WMLs may be categorized as spotty, patchy, confluent, centripetal or centrifugal, or as sub-cortical or central. MIDs with prominent white matter involvement include MELAS, MNGIE, LHON,<sup>111</sup> KSS,<sup>112</sup> Leigh syndrome,<sup>113</sup> NARP,<sup>114</sup> PCH,<sup>115</sup> leukoencephalopathy, brainstem and spinal cord lesions, and lactic acidosis (LBSL),<sup>116</sup> and nsMIDs from a single mtDNA deletion,<sup>117</sup> *tRNA(Trp)*,<sup>118</sup> *ECSH1*,<sup>119</sup> or a *NDU-FAF1* mutation.<sup>120</sup> In a study of 33 genetically confirmed MIDs resulting from mutations in mtDNA located genes, the *SURF1*, and the *POLG1* gene, 18.1% had WMLs.<sup>121</sup>

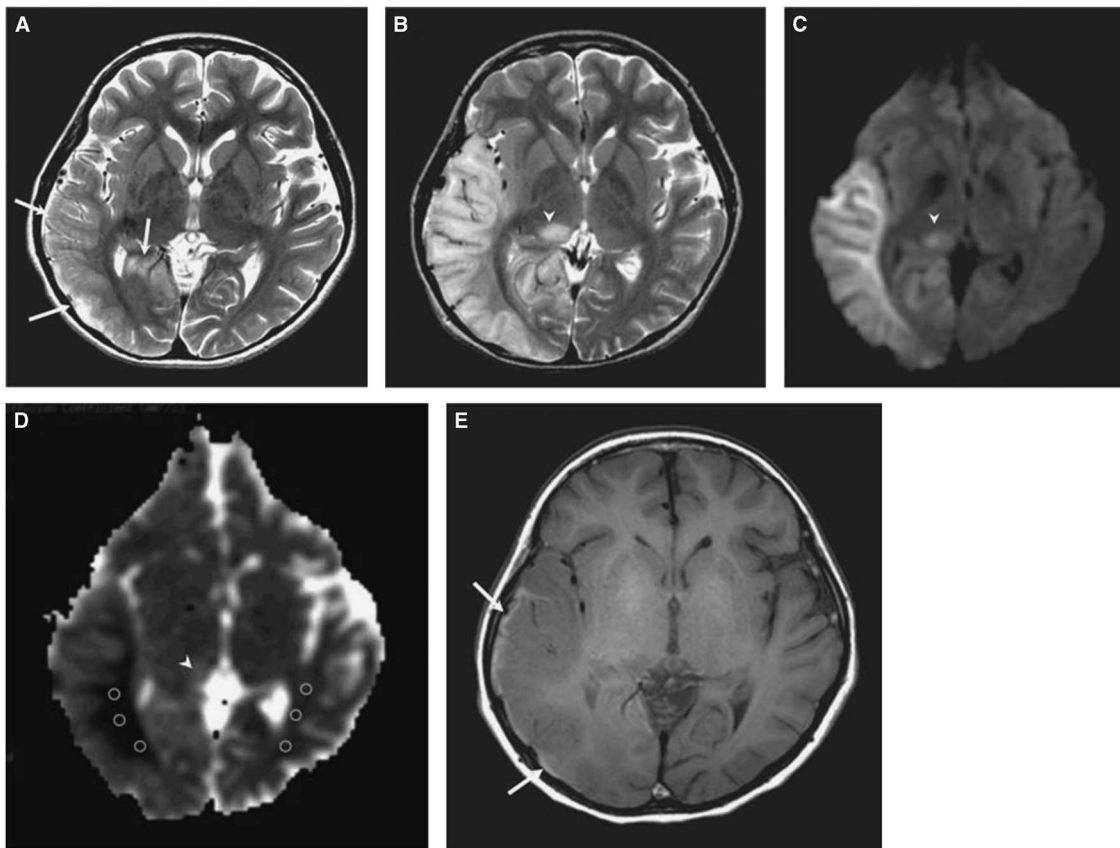
### Gray Matter Lesions

Gray matter lesions may occur as an isolated feature or together with WMLs or other cerebral abnormalities. They may be symmetric or asymmetric. They may be stable, progressive, or regressive over time.<sup>122</sup> Most commonly, gray matter lesions occur in patients with Leigh syndrome.<sup>122</sup> Gray matter lesions in Leigh syndrome show up as T2-hyperintensities of the caudate nucleus, putamen, tegmentum, tectum, periaqueductal area, cerebellum, or pons.<sup>122</sup> The cortical gray matter may be involved in patients with MELAS.<sup>123</sup>

The periaqueductal gray matter can be affected in MERRF in addition to atrophy of the cerebellar pedunculi.<sup>124</sup> Gray matter lesions together with WMLs have been described in MNGIE.<sup>110</sup>

### Atrophy

Atrophy may be diffuse or focal, may affect the supratentorial section or the infratentorial section, may go along with or without clinical manifestations, may be mild or severe, or may be associated with or without other CNS lesions of a MID. Cerebral atrophy occurs in specific MIDs and nsMIDs. Among the specific MIDs, atrophy is particularly prevalent in PCH,<sup>125</sup> CPEO,<sup>126</sup> MELAS,<sup>127</sup> MERRF,<sup>124</sup> PDH deficiency,<sup>128</sup> KSS,<sup>126</sup> and LHON.<sup>129</sup> PCH can even show up as complete agenesis of the corpus callosum.<sup>125</sup> PCH is genetically heterogeneous and can be due to mutations in the *AMPD2*, *DKC1*, *RARS2*, *PCLO*, *VRK1*, *EXOSC3*, *TSEN54*, *CASK*, *TSEN2*, *ALAAS2*, *ABCB7*, or *TET2* genes, respectively. Predominantly cortical atrophy has been reported in patients with CPEO.<sup>130</sup> Pontine and cerebellar atrophy with a hot cross bun sign resulting from the mtDNA deletion m.3264\_1607del12806 may clinically mimic the cerebellar type of multisystem atrophy (MSA-C) manifesting as dysarthria, nystagmus, falls, tremor, impaired coordination, incontinence, dysphagia, or frequent choking.<sup>131</sup>



**Figure 1:** (A) T2-weighted image obtained at day 3 after onset of an SLE shows mild swelling (arrows) of right temporo-occipital lobe. (B) T2-weighted image obtained at day 11 after onset shows progression of edema in the right temporo-occipital lobe and newly appearing thalamic lesion (arrowhead). (C) Hyperintensity of affected areas (arrowhead) on DWI. (D) Hypointensity of the white matter and hyper-/isointensity of the cortex and thalamus on ADC (arrowhead). (E) T1-weighted image shows hyperintense rim (arrows) along cortex of swollen right temporo-occipital lobe, suggesting cortical laminar necrosis. (Reproduced from Kim et al. *Korean J Radiol.* 2011;12:15-24, with permission.)

## Basal Ganglia Calcification

Basal ganglia calcification is a rare phenotypic feature of nsMIDs and often presents without clinical manifestations and is thus often an incidental finding. Basal ganglia calcification may occur unilaterally or bilaterally and in case of bilateral occurrence it may be symmetric or asymmetric. Basal ganglia calcification may or may not be associated with other cerebral or extracerebral manifestations. Basal ganglia calcification is often attributed to non-MID causes and thus neglected as a phenotypic feature of MID. Basal ganglia calcification has been reported in specific and nsMIDs. Among the specific MIDs it has been described in MELAS,<sup>132</sup> Leigh syndrome,<sup>50</sup> and KSS.<sup>133</sup> More frequently, basal ganglia calcification can be found in nsMIDs than in specific MIDs.<sup>134</sup> Basal ganglia calcification may even occur in pediatric patients with MELAS.<sup>135,136</sup> In single cases, basal ganglia calcification was associated with generalized dystonia.<sup>47</sup>

## Hypometabolism

FDG-PET reflects glucose uptake into cells. Reduced uptake into cells reflects hypometabolism within cells. In a study of five patients with Leigh syndrome, of whom four were genetically confirmed, FDG-PET showed hypometabolism in the cerebellum, the basal ganglia, and the temporal lobes.<sup>137</sup> In one patient, hypometabolism was present despite morphologically normal cerebellum on MRI.<sup>137</sup> In a patient with MELAS syndrome manifesting clinically as headache, seizures, and hemianopia to the right, hypometabolism on FDG-PET was demonstrated in both occipital lobes.<sup>138</sup> In two siblings with an MNGIE-like phenotype resulting from multiple mtDNA deletions, but absence of a *TYMP1*, *POLG1*, *ANTI*, or *C10orf2* mutation, FDG-PET showed asymmetric and patchy glucose hypometabolism in the frontotemporal areas.<sup>139</sup>

## Rare CNS Abnormalities in MIDs

Rare CNS abnormalities in MIDs include central sleep apnea syndrome, as has been described in CPEO patients,<sup>140</sup> and optic atrophy. Optic atrophy may be the dominant feature of a MID phenotype or a nondominant feature. As a nondominant feature, optic atrophy has been reported in dilated cardiomyopathy with ataxia syndrome.<sup>141</sup> Only in single cases was auditory agnosia reported as a CNS manifestation of an mtDNA mutation.<sup>142</sup> Microcephaly may be another rare manifestation of a MID, as has been reported in an infant with MELAS syndrome.<sup>143</sup> Rarely, the spinal cord can be affected in nsMIDs manifesting as transverse syndrome, LBSL, or motor neuron disease.<sup>144</sup>

## CONCLUSIONS

This review shows that cerebral manifestations of MIDs can be heterogeneous and occur as isolated clinical manifestations, isolated radiologic/functional abnormalities, or as both. CNS manifestations can be the presenting feature of a MID, which is why CNS abnormalities without conclusive explanation can be indicative of a MID. If only clinical manifestations represent the onset of a MID without abnormalities on imaging or functional studies, suspecting a MID becomes difficult. The suspicion of a MID may be strengthened if there are abnormalities on imaging or functional studies in addition to the clinical manifestations. Imaging studies that strongly suggest a MID include basal ganglia calcification; symmetric gray

matter lesions in the basal ganglia, brain stem, or cerebellum; or SLLs. However, the number of nonspecific findings on imaging, such as WMLs, prevail and are difficult of being attributed to a MID unless more typical manifestations in organs other than the CNS support the suspicion. The reason why certain cerebral regions are predominantly affected is unknown, but there are indications that mutation loads of maternally inherited mtDNA mutations may differ between cerebral regions and that the threshold for clinical manifestations may differ according to the local energy demand. Future studies characterizing more precisely the nature of a clinical or functional/imaging abnormality are required to improve the sensitivity of the workup. In addition to improving the diagnosis of CNS manifestations in MIDs, there is a need to improve the treatment of CNS disease in MIDs, particularly of stroke-like episodes, headache, and mitochondrial movement disorders.

## DISCLOSURES

The authors do not have anything to disclose.

## STATEMENT OF AUTHORSHIP

JF designed the review, organized the literature, and wrote the first draft of the manuscript. EC completed the literature search, supported in the writing, and provided critical comments.

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