Journal of the Neurological Sciences 404 (2019) 29–35

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Review article

Cerebral imaging in adult mitochondrial disorders

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ARTICLE INFO

Keywords:
Respiratory chain
Oxidative phosphorylation
Encephalomyopathy
Mitochondrial
Mitochondrion
Cerebrum
Brain
Spinal cord
Multi-system disease
Central nervous system

ABSTRACT

Objectives: Among the organs/tissues affected in mitochondrial disorders (MIDs), the brain is the second most frequently affected. Cerebral imaging may correlate with clinical findings but not necessarily. This review summarises and discusses current knowledge and recent advances concerning cerebral abnormalities on imaging in adult MIDs (≥18y).

Methods: Systematic literature review.

Results: The most common cerebral abnormalities in imaging in adult MIDs are, as in pediatric MIDs, white matter lesions, grey matter lesions, atrophy, optic atrophy, stroke-like lesions, calcifications, and ischemic stroke. Cerebral lesions may remain stable over years but some may undergo dynamic changes within shorter or longer period of times. Typical dynamic lesions are stroke-like lesions and grey matter lesions in the sense of progression or regression. Since cerebral lesions on imaging may or may not go along with clinical manifestations, it is crucial to screen all MID patients for cerebral involvement, which can be effectively accomplished by application of the MRI.

Conclusions: Cerebral imaging is of paramount importance for diagnosing and monitoring cerebral involvement in MIDs. Cerebral imaging in MIDs contributes to the understanding of the pathogenesis of cerebral involvement in MIDs.

1. Introduction

Mitochondrial disorders (MIDs) are usually multisystem diseases (syndromes) affecting the skeletal muscle, brain [1–3], spinal cord [4], eyes [5], ears, endocrine organs [6], heart [7], and more rarely the lungs [8], liver, pancreas, guts [9], kidneys [10], arteries [11], hematological system [12], immune cells [13], cartilage [14], bones, or the skin [15]. After the muscle, the brain/cord is the second most frequently affected organ in MIDs [3]. Onset of MIDs ranges between birth and senescence and some of the MIDs with onset in infancy, childhood, or adolescence may survive into adulthood. This review aims at summarising and discussing current knowledge and recent advances about abnormalities on imaging of the cerebrum in adult patients with a MID. Compared to previous works, this review provides a systematic overview and classification of all CNS abnormalities so far described in association with MIDs in adults.

2. Methods

We conducted a literature search in PubMed to retrieve studies about adult patients with MIDs in whom cerebral imaging was carried out. Search terms were adult, adulthood, mitochondrial, mitochondrion, mtDNA, combined with brain, cerebral, stroke-like episode, epilepsy, seizure, atrophy, ataxia, movement disorder, white matter lesion, grey matter lesion, calcification, bleeding, toenail sign, eye-of-the-tiger sign, hot cross bun sign, optic atrophy, CCT, CTA, MRI, and MRA. Abstracts of appropriate hits were screened according to the following inclusion criteria: adult patient, genetically or biochemically confirmed MID, application of a cerebral imaging modality. Excluded were patients < 18y, not genetically or biochemically confirmed

Abbreviations: AHD, Alpers Huttenlocher disease; CPEO, Chronic progressive external ophthalmoplegia; CCT, Cerebral compute tomography; DNA, Deoxyribonucleic acid; FLAIR, Fluid-attenuated inversion recovery; GML, Grey matter lesion; KSS, Kearns Sayre syndrome; LBSL, Leucoencephalopathy with brain stem and spinal cord involvement and lactic acidosis; LCN, Laminar cortical necrosis; LHON, Leber's hereditary optic neuropathy; LS, Leigh syndrome; MDS, Mitochondrial depletion syndrome; MELAS, Mitochondrial encephalomyopathy, lactacidosis, stroke-like episodes; MERRF, Myoclonic epilepsy with ragged red fibers; MID, Mitochondrial disorder; MILS, Maternally inherited Leigh syndrome; MIMODS, Mitochondrial multiorgan disorder syndrome; MNGIE, Mitochondrial neuro-gastro-intestinal encephalopathy; MPAN, Mitochondrial membrane protein associated neurodegeneration; MRI, Magnetic resonance imaging; MRS, Magnetic resonance spectroscopy; NARP, Neurogenic muscle weakness, ataxia, and retinitis pigmentosa; PCH-6, Pontocerebellar hypoplasia type-6; PDH, Pyruvat-dehydrogenase; PS, Pearson syndrome; SCA, Spinocerebellar ataxia; SL-episode, Stroke-like episode; SLL, Stroke-like-lesion; WMLs, White matter lesions

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https://doi.org/10.1016/j.jns.2019.07.013
Received 21 April 2019; Received in revised form 6 June 2019; Accepted 9 July 2019
Available online 10 July 2019
0022-510X/

diagnosis, abstracts, proceedings, or articles in languages other than English. We did not include functional studies, such as MRS, SPECT, or PET since they show a uniform pattern in most MIDs (e.g. lactate peak and reduced NAA on MRS) and since they are only rarely applied. Not only original research articles but also review articles were considered.

3. Results

3.1. Number of included articles

After screening the literature, with the search terms mentioned above, 1534 hits were achieved. After exclusion of multiple identical hits, 592 abstracts were assessed for meeting the inclusion criteria. After studying the abstracts, 109 full articles were collected. From 37 abstracts no full article was available. Ten of the full papers were excluded because of imprecise information about the patient's age. Thus, altogether 62 articles were included in this review.

3.2. Adult MIDs

Adult MIDs were defined as those with either facultative onset in adulthood, or pediatric MIDs which survive into adulthood. Generally, patients discussed in this review needed to be ≥18 years of age to be included in this study. MIDs with facultative adult onset include mitochondrial encephalomyopathy, lactacidosis, stroke-like episodes (MELAS), myoclonic epilepsy with ragged red fibers (MERRF), Leber's hereditary optic neuropathy (LHON), Leigh syndrome (LS), mitochondrial neuro-gastro-intestinal encephalopathy (MNGIE), Alpers Huttenlocher disease (AHD), leukoencephalopathy with brain stem and spinal cord involvement and lactic acidosis (LBSL) [16], mitochondrial membrane protein associated neurodegeneration (MPAN), and mitochondrial multiorgan disorder syndrome (MIMODS) (Table 1) [1]. Currently, no specific MIDs with obligatory adult onset are known. Pediatric MIDs which occasionally survive into adulthood include MELAS, MERRF, LHON, chronic progressive external ophthalmoplegia (CPEO), LS, maternally inherited LS (MILS), Kearns Sayre syndrome (KSS), LBSL [17], neurogenic muscle weakness, ataxia, and retinitis pigmentosa (NARP) [18], Pearson syndrome (PS), mitochondrial depletion syndrome (MDS) [19], primary coenzyme-Q (CoQ) deficiency [20], Wolfram syndrome [21], and pyruvat-dehydrogenase (PDH)-deficiency [22].

3.3. Findings on cerebral imaging

Generally, cerebral abnormalities on imaging in MIDs are not at variance from those in pediatric cases but frequency and phenomenology of abnormalities may vary considerably [1]. The most frequent abnormalities on cerebral imaging in adult MIDs include WMLs, GMLs, and atrophy (Table 2). More rarely occurring are optic atrophy, SLLs, calcifications, ischemic stroke, and bleedings. Specific mutations associated with typical CNS abnormalities are listed in Table 3.

Table 1
Number of papers reporting a specific MID and the overall number of patients presented in these articles.

Specific MID	Number of publications	Estimated number of patients
Leigh syndrome	~2000	> 1200
MELAS	~1800	> 1000
AHS	~1500	> 450
LHON	~1000	> 500
KSS	~600	> 500
MERRF	~500	> 350
CPEO	~300	> 900
MNGIE	~200	> 100
NARP	~100	> 50

3.3.1. White matter lesions (WMLs)

A frequent abnormality on cerebral imaging in adult MIDs are the WMLs. WMLs may present with variable configuration, extension, and distribution. With regard to extension, they may present as single or disseminated spots, as confluent or non-confluent patches, or as diffuse lesions. With regard to distribution, WMLs may be focal, disseminated, centripetal, centrifugal, cortical, or subcortical. WMLs may go along with or without other cerebral lesions, particularly GMLs or atrophy. Concerning density, WMLs may be solid or cystic, homogeneous or inhomogeneous [23]. Tissues constituting WMLs include glial cells, fat, edema, calcium carbonate, hematin, or iron. They usually progress but occasionally regression or even resolution of WMLs has been reported [22]. WMLs may be the endpoint of a SLL. WMLs have been most commonly reported in MELAS, LS, LHON, KSS, LBSL, and MIMODS. In a study of 22 adult MELAS patients carrying the m.3243A > G mutation (mean age: 41.2y) with a 7 Tesla MRI, prominent WMLs were detected periventricularly on T1 and T2-weighted images in all patients and grey and white matter volume loss was found compared to age/sex-matched 15 controls [24]. In a 30yo male with slowly progressive gait disturbance, lower limb weakness, and clumsiness of the left hand, cerebral MRI revealed periventricular T2-hyperintensity accompanied by T2-hyperintensity of the entire spine [17]. Work-up revealed a mutation in the *DARS2* gene and the patient was diagnosed with LBSL [17]. WMLs in association with SLLs were also reported in 2 of 34 patients with MERRF syndrome due to the m.8344A > G variant [25]. Bilateral WMLs in the occipital lobes and the cerebellum were reported in a 26yo male with progressive myoclonic epilepsy due to a mutation in the *CARS2* gene [26]. Additionally, global atrophy was noteworthy [26]. In a 31yo male with Wolfram (DIDMOAD) syndrome due to a mutation in the *WFS1* gene, cerebral MRI demonstrated FLAIR-hyperintensity in the peritrigonal areas/optic tracts bilaterally [27].

3.3.2. Grey matter lesions (GMLs)

GMLs may affect the cerebral grey matter, such as the cortex, basal ganglia, or the grey matter in the midbrain, brainstem, or the cerebellum. GMLs may be symmetric or asymmetric and may go along with or without other cerebral lesions (Fig. 3). As with WMLs, GMLs may be progressive or regressive. GMLs may be solid, cystic, homogeneous or inhomogeneous. Tissues constituting GMLs include, glial cells, fat, CSF, edema, calcium carbonate, hematin, or iron. GMLs in adult MIDs particularly occur in LS, LHON, CoQ-deficiency, or in MIMODS. In a 19yo female with AHD due to a *POLG1* mutation, cerebral MRI revealed T2/FLAIR-hyperintensities in the occipital cortex, most prominent in the left hemisphere, with areas of both increased and decreased diffusion on ADC maps [28]. In a study of adult and pediatric patients carrying mutations in the *C12orf65* gene, T2/FLAIR hyperintensities of the thalamus were reported [29]. In a 19yo female with PDH-deficiency due to a mutation in the *PDAH1* gene, and normal intelligence, MRI of the brain showed bilateral lesions of the globus pallidus exclusively, which were hypointense on T1-weighted and hyperintense on T2-weighted images [22]. In a 28yo female with NARP due to the variant m.8993T > C in the *ATP6* gene, cerebral MRI revealed cystic and cavitary T2-hyperintensities in the putamina bilaterally [23]. In a study of 15 adult Turkish probands with MPAN due to mutations in the *C19orf12* gene, cerebral MRI showed symmetric T2-hypointensities in the globus pallidus and the substantia nigra [30]. In a study of 3 Norwegian patients with childhood onset epilepsy and cerebellar ataxia due to mutations in the *ADCK3* gene associated with primary CoQ-deficiency, MRI showed bilateral T2-hyperintensities of the dentate nucleus [20]. In a series of adult and pediatric patients carrying *POLG1* mutations, adults presented with a spinocerebellar ataxia (SCA)-like phenotype, dysarthria, myopathy, neuropathy, and ptosis and subsequent MRIs showed T2-hyperintensities in the postero-lateral thalamus and the occipital lobes [31]. In a 7 Tesla study of 22 adult MELAS patients carrying the m.3243A > G variant (mean age: 41.2y), cortical, subcortical, and cerebellar grey matter volume was significantly reduced

Table 2
MIDs with CNS involvement and faculatitve onset in adulthood (age ≥ 18y) or MIDs with CNS involvement surviving into adulthood.

Syndrome	Onset	CNS-abnormality
Facultative onset in adulthood		
MELAS	Infancy to adulthood	WMLs, GMLs, SLLs, atrophy, calcifications, stroke
MERRF	Infancy to adulthood	SLLs, atrophy, cysts
LHON	Childhood to adulthood	WMLs, GMLs, atrophy, optic atrophy
LS	Birth to adulthood	Symmetric GMLs
MNGIE	1st-5th decade	WMLs
AHS	2-24y	WMLs, GMLs
LBSL	Infancy to adulthood	WMLs, atrophy
MPAN	Childhood to adulthood	GMLs
MIMODS	Infancy to adulthood	WMLs, GMLs, atrophy, calcifications
Occasionally survival into adulthood		
MELAS	Infancy to adulthood	WMLs, SLLs, atrophy, calcifications
MERRF	Infancy to adulthood	SLLs, atrophy, cysts
LHON	Childhood to adulthood	WMLs, GMLs, atrophy, optic atrophy
CPEO[a]	Birth to 15y	SLLs, atrophy
KSS	2-16y	WMLs, SLLs, atrophy, calcifications
PS	1-9y	CSF protein ↑
LS	Birth to adulthood	Symmetric gey matter lesions
MILS	Infancy, childhood	GMLs
LBSL	Infancy to adulthood	WMLs, atrophy
NARP	Infancy, childhood	WMLs, atrophy, calcifications
MDS	Infancy, childhood	Atrophy, cysts
IOSCA	Infancy	Optic atrophy, hypometabolism (PET) [59][a]
HBSL	Infancy to adulthood	WMLs [60][a]
FBSN	Infancy	Bilateral striatal necrosis [61][a]
Coenzyme-Q deficiency	Infancy, childhood	GMLs [20][a]
Wolfram syndrome	Infancy, childhood	Optic atrophy [21][a]
PDH-deficiency	Infancy, childhood	GMLs [22][a]
NBIA	Infancy to adulthood	Cerebral iron accumulation [62][a]

[a] Paper, in which survival into adulthood is decsribed.

Table 3
CNS abnormalities associated with the most frequent mtDNA and nDNA mutations.

Mutation	CNS abnormalities
m.3243A > G	SLE, WMLs, GMLs, atrophy, calcifications, ischemic stroke
m.8344A > G	SLLs, atrophy, cysts
m.3460G > A	WMLs, GMLs, atrophy, optic atrophy
m.11778G > A	WMLs, optic atrophy
m.14484T > C	WMLs, optic atrophy
m.8993T > C	WMLs, symmetric GMLs, atrophy, calcifications
m.8993T > G	WMLs, symmetric GMLs
POLG1	WMLs, atrophy, SLLs

and the ventricular volume significantly increased compared to 15 age/sex-matched controls [24]. In children with LS spontaneous, complete resolution of the GMLs has been reported in some of them [32]. In an 18yo male with MPAN, manifesting as predominant lower limb spasticity, generalised dystonia, and cognitive impairment, due to a mutation in the *C19orf12* gene, imaging of the brain by MRI revealed iron deposition in the globus pallidus and substantia nigra but no eye-of-the-tiger sign [33]. The eye-of-the-tiger sign has been nonetheless reported in pediatric and adult patients with GRACILE syndrome due to mutations in the *BCS1L* gene [34].

3.3.3. Atrophy

Atrophy is a frequent cerebral abnormality in adult MID patients. It may be primary due to loss of neurons or glial cells, demyelination, or hypoplasia. It may be secondary following a SLL, ischemic stroke, or bleeding.

Atrophy may be focal or generalised, cortical or subcortical, supratentorial or infratentorial. Generally, focal atrophy is more frequent than generalised atrophy. It may go along with or without clinical manifestations and with or without other cerebral lesions. Atrophy may concern grey and white matter simultaneously. Atrophy may be stable or progressive but resolution of atrophy has not been reported.

3.3.3.1. Supratentorial. In a study of 8 patients carrying *POLG1* mutations, diffuse cortical atrophy occurred in one third of them [35]. Global cerebral atrophy was found in a 40yo male with MERRF syndrome due to the variant m.4279A > G in the *tRNA(Ile)* gene [36]. In a study of 34 patients with MERRF due to the variant m.8344A > G cerebral or cerebellar atrophy was found in 43% of the patients undergoing cerebral MRI [24]. Focal atrophy may also concern the basal ganglia, the corpus callosum, the frontal, parietal, temporal, or the occipital lobes. Partial agenesis of the corpus callosum has been reported in patients carrying *C12orf65* mutations [29].

3.3.3.2. Brainstem, cerebellum. Cerebellar atrophy may concern the pedunculi, the vermis, the hemispheres, the cortex, the cerebellar nuclei, or the entire cerebellum [37]. It may go along with hyperintensities of the dentate or olivary nuclei [37]. MIDs which typically manifest with focal or global cerebellar atrophy include KSS, CPEO, NARP, LHON, MERRF, LBSL, LS, AHD, and MIMODS [1]. In a 28yo female with NARP due to the variant m.8993T > C in the *ATP6* gene, moderate diffuse atrophy of the cerebellum bilaterally has been reported [23]. In a case report about a 26yo male with NARP syndrome due to the variant m.8993T > G, cerebral MRI revealed severe diffuse cerebellar atrophy and mild cerebral atrophy [18]. Generalised atrophy with predominance of the cerebellum and the brainstem was reported in a 31yo Japanese female with NARP due to the variant m.8729G > A, manifesting as progressive limb muscle weakness with distal predominance, cerebellar ataxia, hypoesthesia, myoclonus, and hypoacusis [38]. In a 33yo female with a MSA-C-like phenotype, cerebral MRI showed marked atrophy of the pons and cerebellum and a hot cross bun sign, which is typical for MSA-C [39]. In fact, the patient carried a single mtDNA deletion and was re-diagnosed as MIMODS [39].

3.3.4. Optic atrophy

Another focal type of atrophy in MIDs is optic atrophy. Atrophy of the optic nerve has been particularly reported in LHON, ADOA (*OPA1* mutations), other optic atrophy spectrum disorders [40], and MIMODS. In patients carrying *C12orf65* mutations, optic atrophy was a dominant feature of the phenotype in addition to progressive encephalopathy, neuropathy, and spastic paraparesis [29]. Patients carrying *OPA1* mutations may manifest with cerebral abnormalities in addition to optic atrophy, such as cerebellar atrophy mainly including the vermis, non-specific WMLs, and cortical atrophy [41]. Patients with abnormal MRI were older, had more severe visual impairment, and more frequently deafness than those with normal MRI [41]. In a study of 35 patients carrying an *MTO1* mutation, 52% had optic atrophy in addition to MIMODS [40]. Optic atrophy is a dominant phenotypic feature of Wolfram syndrome, which is due to mutations in the *WFS1* gene [42]. Wolfram syndrome additionally presents with diabetes mellitus, diabetes insipidus, and deafness [27]. Atrophy of brainstem and cerebellum can be severe in Wolfram syndrome [27].

3.3.5. Stroke-like lesions

3.3.5.1. Characteristics. SLLs are the morphological equivalent of stroke-like episodes, a hallmark of MELAS (Fig. 1). However, SLLs do not exclusively occur in MELAS but may be also found in other conditions, such as MERRF [25], KSS, LS, Saguenay-Lac-St.-Jean cytochrome oxidase deficiency, MELAS/LS overlap syndrome, LHON, or CPEO. SLLs are the most dynamic lesions among brain lesions in MIDs. SLLs can be most accurately detected by application of the MRI and less accurately by CCT. SLLs present heterogeneously with regard to morphology, extension, and dynamics, why it is often difficult to identify them as such. In the vast majority of the cases, it may go along with clinical manifestations, but rarely they may be asymptomatic. The most consistent characteristic of SLLs is the fact that they are not confined to a vascular territory. All other features characterising SLLs are fairly inconsistent. SLLs occur most frequently in an occipito-temporal distribution but every other cerebral region can be also affected. SLLs may in a monolocal or multilocal distribution. Stroke-like episodes (SLEs), the clinical manifestations of a SLL, are more frequent in pediatric as compared to adult MIDs.

3.3.5.2. Stages and course. An acute stage and a chronic stage of SLLs can be delineated. The acute stage of SLLs goes along with clinical manifestations whereas the chronic stage of a SLL may go along without or only mild clinical manifestations. In the acute stage, SLLs expand but regress in the chronic stage. With regard to perfusion, there is hyperperfusion in the acute stage and hypoperfusion in the chronic stage. Hyperperfusion may occur already weeks prior to the clinical onset of a SLE [43]. Hyperperfusion and hypoperfusion can be demonstrated by PWI or SPECT. Acute SLLs most frequently present as vasogenic edema, thus they are hyperintense on DWI and hyperintense on ADC but also cytotoxic edema (hyperintense on DWI and hypointense on ADC) has been described [44]. The vasogenic/cytotoxic edema undergoes dynamic changes on from onset such that it expands in extension and regresses in the chronic stage. In the chronic stage the ADC usually becomes isointense (Table 4). However, a common pattern according to which SLLs develop over time has not been characterised thus far. The chronic stage is characterised by a similar but variable pattern as in the acute stage. SLLs may end up as normal brain, WMLs, cystic changes, atrophy, laminar cortical necrosis, or the black toenail sign [45]. The black toenail sign signifies gyral necrosis best visualised on T2/FLAIR sequences [45]. SLLs frequently recur. In a 37yo female with MELAS due to the variant m.3242A > G an acute SLL in the occipito-temporal distribution was hypointense on T1-weighted images, FLAIR hyperintense, DWI-hyperintense, and ADC-hypointense, which did not enhance after gadolinium application [44]. In a 55yo Japanese male with cortical blindness, epilepsy, and severe cognitive impairment due the *ND3* variant m.10158T > C, cerebral MRI revealed recurrent SLLs in different cerebral locations within 7 months after onset, which were hyperintense on DWI and hyperintense on ADC in the acute stage [46].

Table 4
Characteristics of the acute and chronic stage of SLLs.

Item	Acute	Chronic
Dynamics	Expanding	Regressing
Clinical manifestation	Yes	None or few
DWI	Hyperintense	Hyper/iso/hypointense
ADC	Hyper/hypointense	Iso/hypointense
PWI/SPECT	Hyperperfusion	Hypoperfusion
OEF MRI	Reduced	Normal

OEF: oxygen extraction fraction.

3.3.6. Calcifications

Calcifications are rarely reported in the brain of MID patients. In all patients reported, they occurred in a focal distribution. Calcifications may be symmetric or asymmetric. They may or may not go along with other cerebral or clinical manifestations. Most frequently calcifications of the basal ganglia are reported in MID patients (Fig. 2). Less frequently, calcifications of the dentate nucleus or the cerebellum were

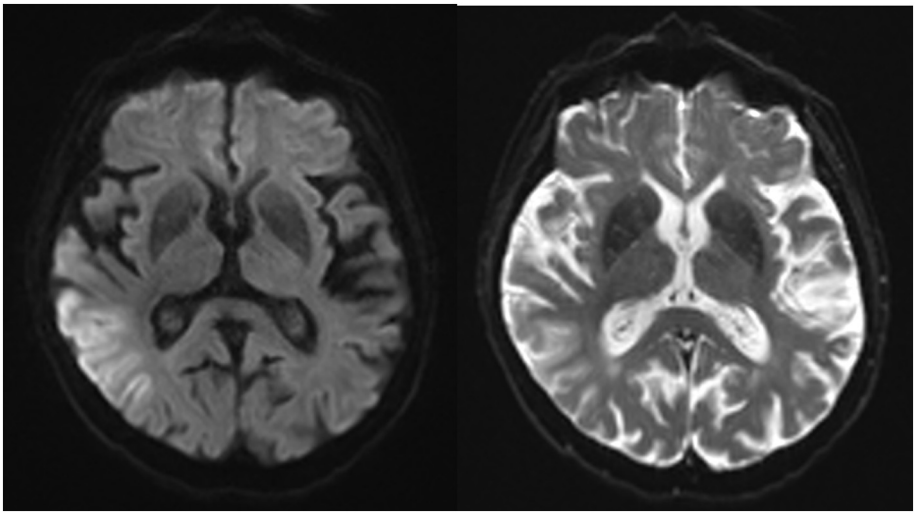

Fig. 1. Typical right SLL with occipito-temporal distribution in a female with MELAS showing up as hyperintensity on DWI and hyperintensity on ADC.

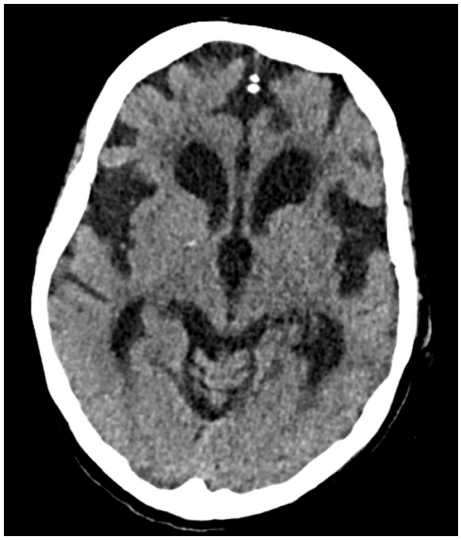

Fig. 2. Cerebral CT scan of a female with MIMODS (epilepsy, dementia, hemiplegia, cardiomyopathy, heart failure, renal insufficiency) showing severe global atrophy with frontal predominance and basal ganglia calcification bilaterally.

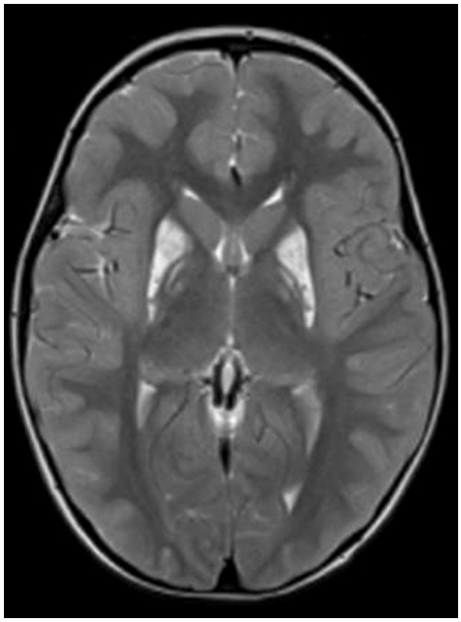

Fig. 3. T2 supra-orbital MRI of a patient with Leigh syndrome due to the ND3 variant m.10134C > A showing symmetrical bilateral cystic gliosis within the globus pallidus (orange arrows). [reporduced from Miller et al. PlosOne 2014].

reported. Basal ganglia calcifications can be most frequently observed in patients with MELAS and KSS [1]. Calcifications may concern the grey as well as the white matter in isolation or simultaneously.

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3.3.7. Ischemic stroke

Since MIDs may also manifest in the arteries [11], secondary ischemic stroke may ensue in case of carotid artery or intracerebral artery stenosis, occlusion or dissection. Occasionally, Moya Moya syndrome, due to bilateral occlusion of the distal, supraclinoidal parts of the internal carotid arteries may occur [47]. Mitochondrial arteriopathy may be primary in case of affection of the endothelial cells, vascular smooth muscles cells, or the adventitia by the underlying metabolic defect. Mitochondrial arteriopathy may be secondary in case of diabetes, hyperlipidemia, or arterial hypertension, all well-known manifestations of a MID. Secondary ischemic embolic stroke may additionally result from affection of the heart by atrial fibrillation, by severe heart failure due to dilated cardiomyopathy, or by noncompaction. Noncompaction is a cardiac abnormality frequently associated with MIDs. It is characterised by hypertrabeculation, most frequently of the left ventricular apex and the lateral wall, and is associated with an increased risk of cardio-embolism. It needs to be prospectively excluded in MIDs since it is subclinical in the majority of the cases. Noncompaction can be complicated by heart failure, stroke/embolism, or ventricular arrhythmias, including sudden cardiac death. MIDs are the disorders in which noncompaction can be most frequently found [48].

3.3.8. Bleedings

Intracerebral bleeding (ICB) in MIDs is rare [49]. Causes of ICBs in adult MID patients could be arterial hypertension, a frequent manifestation of MIDs, arteriovenous malformations, cavernomas, SLLs, and ischemic stroke. Whether recurrent SLLs in patients with MELAS represent a risk factor for ICB is currently speculative. In MELAS patients with dissection of the intracerebral arteries mitochondrial cytopathy was detected in the walls of micro-vessels representing a possible source of vulnerability and cause of microhemorrhaghes [50]. Another source of bleeding could be aneurysm formation, which seems to be more prevalent in MIDs than in the general population [51]. Recently, the bleeding tendency in MELAS was explained by the development of antifibrinogen antibodies, being attributed to the frequent association of MIDs with autoimmune disorders [52]. A fatal ICB has been reported in a 39y Japanese male with MELAS/MERRF overlap syndrome due to the variant m.8356T > C in the *tRNA(Lys)* gene [49]. Post mortem investigations of the brain did not disclose any source of bleeding in this patient [49]. Putaminal bleeding in a 48yo male with MERRF syndrome has been reported by Huang et al. [53]. Recurrent cerebral haemorrhage was reported in a 44yo female with MELAS by Penisson-Besnier et al. [54]. In a study of 6 patients with MELAS, aged 23 to 68y, one patient developed intracortical gyral hemorrhaghe being attributed to disruption of the blood brain barrier [55]. In another patient of this series petechial gyral micro-hemorrhaghes were found on autopsy [55]. In a 21yo male with suspected adult LS post mortem investigations revealed multiple hemorrhaghes [56]. Retinal hemorrhaghes were reported in adult patients with LHON [57]. Spontaneous hemispheric cerebellar bleeding occurred also in a previously asymptomatic 37yo male carrier of the variant.3243A > G [58].

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4. Conclusions

Since the brain is frequently affected in adult MIDs, it is important that these patients undergo cerebral imaging. Not only patients with clinical manifestations of a cerebral lesion should undergo a cerebral MRI, but also asymptomatic patients. With progression of the disease, initially asymptomatic cerebral lesions may become symptomatic over time. The most frequent abnormalities in adult MIDs are WMLs, GMLs, and focal atrophy. SLLs seem to occur less frequently in adults as compared to pediatric MIDs. The reason why imaging abnormalities in adult MIDs vary from those in pediatric MIDs is that the cerebral abnormalities can be progressive and may become more extensive in adulthood or that co-pathologies of the cerebrum become more prevalent with age and may trigger or enhance pre-existing genetic abnormalities. Due to the potentially longer disease duration in adults, atrophy, WMLs, and GMLs may be more pronounced in case they were progressive. To assess cerebral involvement in adult MIDs it will be useful to apply MRI with high resolution in addition to techniques which assess cerebral perfusion and metabolism, such as SPECT and PET. To assess cerebral arteriopathy in MIDs any type of angiography will help to elucidate the frequency of cerebral macroangiopathy in MIDs. Mechanisms underlying the neuroradiological changes discussed

above include apoptosis, necrosis, ischemia, and metabolic breakdown. Why certain neuroradiological features occur more frequently in some patients than in others could be explained by the pattern of multiorgan involvement and the specificity of the metabolic defect. For example, patients with additional hyper-parathyroidism may be more prone to basal ganglia or other cerebral calcifications than patients who have no endocrine involvement. Metabolic defects affecting the calcium-homeostasis of mitochondria may more likely present with cerebral calcifications than those without affection of the calcium-metabolism. Thus, mutation type may determine the neuroimaging phenotype but variability of this phenotype between patients carrying the same mutation may depend on mutation load, haplotype, and frequency and type of polymorphisms. Accordingly, mutation type may be the reason why SLLs predominantly occur in MELAS, which is due to the m.3243A > G variant in about 80% of the cases. The reason why some cerebral regions are more severely or predominantly affected than others could be also explained by heteroplasmy rates which randomly differ between cell types but also because a specific metabolic defect may have different consequences depending on the specification of a cell. There is no general timeline with regard to the sequence according to which CNS lesions in MIDs develop. In some patients with Leigh syndrome, for instance, GMLs occur prior to the occurrence of WMLs but it can be the other way round in other patients. Since the genetic background of MIDs is extremely heterogeneous and highly individualised due to the random distribution of mutation loads in mtDNA related MIDs, development of certain cerebral lesions may not follow a general pattern but may rather change from patient to patient, at least in this group of MIDs. Cerebral lesions in MIDs due to an nDNA variant may follow a more general pattern, as can be seen in patients with Leigh syndrome carrying pathogenic nDNA variants.

Ethics approval and consent to participate

Not relevant.

Consent for publication

Not relevant.

Availability of data and material

Not relevant.

Funding

No funding was received.

Author contributions

JF: design, literature search, discussion, first draft, final approval.

Authors' information (optional)

None.

Declaration of Competing Interest

There are no conflicts of interest.

Acknowledgements

None.

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