



# Genetic causes of acute encephalopathy in adults: beyond inherited metabolic and epileptic disorders

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## Abstract

Acute encephalopathy is a widely used term, implying a rapidly progressive multifocal or diffuse brain dysfunction, caused by acute structural disturbance or a myriad of metabolic, toxic, epileptic, or infection-related factors. Apart from the more common acquired causes, a broad range of rare inherited disorders may produce spells of encephalopathy in adulthood, posing diagnostic challenges to clinicians. Among the latter, neurometabolic disorders and epileptic syndromes constitute typical examples. Interestingly, certain genetic entities have the potential to provoke episodic changes of cognition, via alternative, neither metabolic nor epileptic, mechanisms. Our aim is to provide a short and focused overview of their clinicoradiological features and potential pathophysiology. As the neurogenetic landscape is rapidly evolving, it is important to be familiar with these chameleons, in order to provide swift diagnosis and proper genetic counselling.

## Highlights

- **Approaching a patient with episodic impairment of consciousness is one of the most demanding tasks in the field of clinical neurology.**
- **After excluding common and uncommon acquired causes of acute encephalopathy, one should always think of the genetic variants.**
- **Among the latter, encephalopathies of metabolic origin due to enzymatic deficiency or mitochondrial dysfunction are commonly analyzed in the literature.**
- **Certain genetic diseases without evidence of metabolic alteration or epileptic component should also be considered in differential diagnosis, principally in terms of genetic counselling and preventing, or treating disabling attacks.**

**Keywords** Encephalopathy · Metabolic disease · Paroxysmal disorder · Genetic

## Introduction

The term encephalopathy stems from the Greek word “*εγκεφαλοπάθεια*,” meaning passion or suffering (“*πάθος*”) of the brain (“*εγκέφαλος*”). Recently, a task force group of experts from ten academic societies provided a consensus-based, uniform nomenclature in the field of acute cognition disturbances [1]. They recommended that the term acute encephalopathy should be considered as a rapidly

developing pathophysiological brain process, which may be expressed as either subsyndromal delirium, delirium, or coma [1]. According to this position statement, subsyndromal delirium refers to an intermediate state between normal cognition and delirium, where not all DSM-5 criteria for delirium are fulfilled.

We would like to clarify that the epileptic encephalopathies of genetic origin are beyond the scope of this review, since they constitute a conceptually distinct group of disorders, necessitating separate study. In these cases, the epileptiform activity itself is the fundamental factor in the development of mental impairment or developmental regression beyond what might be anticipated from the responsible pathology [2]. In other words, the term epileptic encephalopathy refers mostly to the long-term cognitive consequences of a catastrophic epileptic disorder.

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Among causes of encephalopathy, inherited metabolic disorders represent major culprits, emphatically in neonates, infants, and children [3]. In particular, organic acidurias, beta-oxidation defects, aminoacidopathies, homocysteine remethylation defects, and biotin-thiamine-responsive basal ganglia disease have all been associated with relapses of disturbed consciousness [4, 5]. Adult neurologists may similarly face exceptional cases of delirium or coma in the context of a genetic metabolic abnormality. Classic examples comprise urea cycle disorders (e.g., due to ornithine transcarbamylase deficiency) and hepatic porphyrias (e.g., due to porphobilinogen deaminase deficiency) (Table 1) [6, 7]. In these paradigms, the biochemical defect becomes neurologically apparent, whenever an

identifiable precipitant, such as an increased protein load; a physiological stress, such as an intercurrent illness or surgery; or certain medications, induces a substantial metabolic decompensation [3].

Over the past years, it became apparent that various diseases having a diverse genetic substrate may lead to acute encephalopathy in adults without evidence of metabolic or epileptic component that could explain this presentation. Unraveling these disorders represents a diagnostic challenge, given their rarity and clinician unfamiliarity. To our knowledge, there has been no focused and comparative review of their characteristics. Our ambition is to fill in this gap in the literature (Tables 2 and 3), rendering them more easily identifiable in neurological practice.

**Table 1** Inherited, metabolic disorders with potential to cause acute encephalopathy in adults

	Wilson's disease	Acute porphyrias	Urea cycle disorders	Biotin-responsive basal ganglia disease
Age	Children Young adults	Young adults	Infancy, children Rarely in adults	Infancy, children Rarely in adults
Gene(s)	ATP7B	HMBS, PPOX, CPOX, ALAD	CPS1, OTC, ASS1, ASL, SLC25A15	SLC19A3
Encephalopathy characteristics	Hepatic encephalopathy in the setting of acute liver failure	In up to 70% of porphyric attacks May simulate PRES	Often triggered by protein load or stress Hyperammonemic crisis	Resembles Wernicke-type encephalopathy
Prognosis	Poor	Good	Good if treated	Good
Treatment	Liver transplantation	I.V. hemin Symptomatic, prophylaxis	Hemodialysis Sodium benzoate Prophylaxis	Biotin-thiamine supplementation Symptomatic

*ATP7B* ATPase copper transporting beta, *HMBS* hydroxymethylbilane synthase, *PPOX* protoporphyrinogen oxidase, *CPOX* coproporphyrinogen oxidase, *ALAD* aminolevulinic acid dehydratase, *CPS1* carbamoyl-phosphate synthase 1, *OTC* ornithine transcarbamylase, *ASS1* argininosuccinate synthase 1, *ASL* argininosuccinate lyase, *PRES* posterior reversible encephalopathy syndrome.

**Table 2** Summary of the main clinical features of the encephalopathy attacks in inherited, non-metabolically related, disorders

	VWM	NIID	CADASIL	CMTX	FHM	ANE	HLH	MELAS/ POLG	MERS
Age	1–8 years peak 20% teens- adults	Adults	Young to mid-age adults	Children- young adults	Youth	Children Young adults	All ages	Children Adults	All ages
Trigger	Inf, head injury Anesthesia	None	None	High altitude Infection	Head trauma Angiography	Viral inf	Inf	Inf, dehydra- tion, fasting, seiz	Viral, metabolic disease
Relapses	y	-	y	y	y	y	-	y	Rare
Prognosis	Poor	Unknown	Excellent	Excellent	Moderate	Moderate	Poor	Moderate	Good
Treatment	None	Steroids?	Symptomatic	None	Symptomatic prophylaxis	Steroids- IVIG	Steroids HCT	Symptomatic prophylaxis	Symptomatic

*ANE* acute necrotizing encephalopathy; *CADASIL* cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; *CMTX* X-linked Charcot-Marie-Tooth disease; *FHM* familial hemiplegic migraine; *HCT* hematopoietic cell transplantation; *HLH* hemophagocytic lymphohistiocytosis; *Inf* infections; *MERS* mild encephalitis/encephalopathy with a reversible splenic lesion; *NIID* neuronal intranuclear inclusion disease; *MELAS/POLG* mitochondrial encephalopathy; lactic acidosis and stroke-like episodes/polymerase gamma disease; *seiz* seizures, *VWM* vanishing white matter disease.

**Table 3** Genetic aspects of non-metabolic diseases leading to acute encephalopathy

Disorder	Gene(s)	Molecular pathogenesis	Inheritance	Estimated prevalence
MELAS	mtDNA (typically MT-TL1 and MT-ND5); other mt DNA genes	Decreased function of respiratory chain complexes or constituent subunits	Mitochondrial	Varies between population (i.e., 16:100,000 in Finland)
POLG-related disease	POLG	Disturbance of mtDNA replication	Autosomal recessive	1:10,000 (Northern Europe)
CADASIL	NOTCH3	Aggregation of mutant NOTCH3 protein in cerebral vasculature	Autosomal dominant	5:100,000 (underdiagnosed)
CMTX	GJB1	Reduced efficiency of gap junctions between oligodendrocytes and astrocytes in CNS	X-linked	2:100,000
VWM	EIF2B1-5	Dysfunction of the cellular stress response pathway	Autosomal recessive	1,4: 1,000,000
FHM	CACNA1A, ATP1A2, SCN1A	Increased susceptibility to cortical spreading depression	Autosomal dominant	3: 100,000
NIID	NOTCH2NLC (repeat expansion)	Accumulation of intranuclear ubiquitinated neuronal inclusions	Autosomal dominant	Unknown, possibly restricted to East Asian populations
ANE	RANBP2	Altered immune response to viruses	Autosomal dominant	Unknown, mostly in East Asia
HLH	PRF1, STX11, STXBP2, UNC13D	Deficiency in cytotoxic pathways	Autosomal recessive	1:100,000
MERS	MYRF	Myelin vacuolization	Autosomal recessive	Extremely rare

*MELAS* mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; *POLG* polymerase gamma; *CADASIL* cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; *CMTX* X-linked Charcot-Marie-Tooth disease; *VWM* vanishing white matter disease; *FHM* familial hemiplegic migraine; *NIID* neuronal intranuclear inclusion disease; *ANE* acute necrotizing encephalopathy; *HLH* hemophagocytic lymphohistiocytosis; *MERS* mild encephalitis/encephalopathy with a reversible splenic lesion.

## Methods

Data for this review were obtained by searches of MEDLINE for references of relevant articles. Search terms used were “encephalopathy”, “acute encephalopathy”, “coma”, “stupor”, “adulthood”, “metabolic disease”, “inborn errors of metabolism”, “inherited metabolic disorders”, “genetic encephalopathies”. Results were then screened for potentially relevant studies by application of inclusion and exclusion criteria for the full texts of the papers. Randomized controlled trials; observational, controlled studies of case series; and case reports were included. Only original, peer-reviewed articles about humans published in English between 1975 and 2020 were analyzed. Reviews and editorials were also considered. Websites checked for additional, particularly genetic information, were the following:

Neuromuscular homepage: <https://neuromuscular.wustl.edu/> and.

Genetics Home Reference: <https://doi.org/10.1016/j.jns.2019.03.021>

## Vanishing white matter disease

Leukoencephalopathy with vanishing white matter (VWM) is an autosomal recessive disease caused by mutations in any of the five EIF (eukaryotic initiating factor) 2B genes [8]. Several lines of evidence suggest that VWM represents a developmental disorder of glial cells driven by astrocytic pathology [9]. VWM leads to progressive motor, cognitive, and psychiatric disability, along with seizures, whereas brain imaging discloses a distinct pattern of abnormalities, namely, cystic-like regions (hypointense on T1 and FLAIR) evoked by rarefaction of white matter within confluent areas of T2 supratentorial hyperintensities [8, 10].

The disease affects predominantly infants and young children; however, adolescent and adult onset are remarkable in approximately 25% of all cases [11]. A defining characteristic of VWM that facilitates its recognition from other leukodystrophies is the occurrence (even at the outset of the disease) of discrete episodes of neurological deterioration superimposed on a background of chronic progressive course [11, 12]. According to natural history data from

multicenter, longitudinal studies, the episodes involve motor problems and cognitive disturbance, whereas in nearly 60% of cases they consist of confusion or coma [11, 12]. Typical provoking factors of these crises in descending order of frequency include febrile illness, minor head injury, subclinical infections, anesthesia, acute psychologic stress, hyperthermia, and seizures [8–10].

Recent progress in the understanding of VWM pathomechanisms suggests that this selective susceptibility to various stimuli is mediated by the dysregulation of the integrated stress response, caused by the EIF2B mutations [13]. We emphasize that acute events in VWM are commonly followed by severe handicaps or, in rare cases, even death. Therefore, treating neurologists, who may examine adolescents or adults with genetically confirmed VWM, should focus on the primary prevention and/or early symptomatic treatment of the attacks.

### **Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)**

Most clinical neurologists are familiar with this genetic vascular leukoencephalopathy, characterized by mid-adult onset of recurrent ischemic strokes and cognitive impairment progressing to dementia. Useful pointers to a probable CADASIL diagnosis is a positive personal history of migraine with aura and the indicative imaging findings of small vessel angiopathy, including prominent involvement of the anterior temporal pole and the external capsule [14]. Typically, CADASIL is caused by missense mutations of the NOTCH 3 gene, producing a cysteine amino acid change in one of the epidermal growth factor repeat domain of the extracellular part of the NOTCH 3 protein [14, 15].

Interestingly, a minority of CADASIL patients exhibits episodes of acute and reversible encephalopathy, as first suggested by case reports published in 2002 [16, 17]. Subsequently, the term CADASIL coma was coined to these events by Schon et al [18]. In their series of patients, six out of 70 individuals presented with an encephalopathy, originally perceived as acute encephalitis.

Recently, the clinical features, risk factors, neuroimaging correlates, and prognosis of CADASIL encephalopathy from a large British cohort have been delineated. In agreement with the previous mentioned study, acute events affected nearly 10% of the population studied. In sharp contrast to VWM, no specific provoking factors were identified [15].

Migrainous symptoms prevail at the onset of the deteriorating events and gradually give rise to consciousness alteration of variable level. The encephalopathy period is then dominated by focal neurological signs, mostly of cortical origin, and less frequently by visual hallucinations and epileptic seizures. Unlike VWM, complete recovery is observed

within 1–3 months in the vast majority of patients, whereas relapses are noted in one-third of them. Regarding neuroimaging, no overt signs of ischemic changes were detected during the acute phase of the encephalopathy period. Of note, a minority of MR studies revealed focal cortical swelling indicating mild cerebral edema [15].

According to this study, a past history of migraine with aura is the major risk factor for the development of encephalopathy. Overall, the close association with migraine provides some indirect evidence that mechanisms, such as cortical spreading depression, might be implicated, although the exact pathophysiology is currently unknown [19].

### **Neuronal intranuclear inclusion disease**

Neuronal intranuclear inclusion disease (NIID) is a slowly progressive neurodegenerative disorder defined pathologically by the presence of eosinophilic hyaline intranuclear inclusions in the central, peripheral, and autonomic neurons [20]. NIID has a wide clinical spectrum consisting of cognitive problems, cerebellar ataxia, pyramidal-extrapyramidal signs, peripheral neuropathy, and autonomic dysfunction. Until recently, the chance of diagnosing NIID during life was small, because of its protean clinical manifestations, the absence of reliable biomarkers and the absolute need to proceed to invasive procedures, such as brain biopsy [21].

Fortuitously, a multicenter study from Japan confirmed earlier observations that skin biopsy may enable ante mortem diagnosis of NIID by identifying inclusion in adipocytes and sweat gland cells morphologically and immunohistochemically identical to those found in the CNS [21–23].

In the above-mentioned study of 57 adult NIID cases, those with sporadic disease had invariably developed dementia, whereas neuropathy was the prominent manifestation in the younger, familial subgroup of patients. Notably, 20% of sporadic NIID patients suffered subacute encephalitic-like episodes, composed of fever, vomiting, and confusion. Some of these patients showed focal brain edema and gadolinium enhancement on MR scans, while they benefited moderately from steroid pulse therapy [21]. Whereas the nature of these episodes is unclear, Fujita et al. reported on SPECT perfusion changes similar to those found during migraine with aura in a single NIID case [24].

It is also of major clinical importance that the vast majority of NIID subjects demonstrate a selective pattern of high signal abnormality on diffusion-weighted images involving the U fibers along the corticomedullary junction, thus facilitating NIID diagnosis [21, 22]. With the advent of human genetics and the recent discovery of a novel trinucleotide repeat expansion in the human-specific NOTCH2NLC gene as the genetic background of NIID, we believe that this disorder will be more frequently identified in neurology clinics [25, 26].

## X-linked Charcot-Marie-Tooth disease

X-linked Charcot-Marie-Tooth (CMTX1), emerged as one of the most prevalent subtypes of CMT disease, is caused by pathogenic variants in GJB1 gene encoding connexin32 (Cx32) [27]. It has been clearly documented in the literature that a significant minority of CMTX1 patients may, in addition, display signs of CNS dysfunction, detected through clinical, radiological, or neurophysiological testing [28–31]. Furthermore, subjects carrying certain mutations of GJB1 gene are prone to develop stroke or ADEM-like episodes comprising transient hemiparesis, paraparesis, quadriparesis, ataxia, dysarthria, and dysphasia [31–34]. These fully reversible symptoms have been consistently linked with diverse triggers, like traveling to high altitude, febrile illness, trauma, and hyperventilation. CNS events tend to be more common in children and young adults without any correlation with the stage and severity of the peripheral neuropathy [31].

Short-term or persistent confluent areas of T2 high signal in the deep white matter and more rarely in the corpus callosum, occasionally showing restricted diffusion, constitute the radiological accompaniments of the episodes [27, 31]. From a pathophysiological point of view, in vivo and in vitro disease models have indicated that the disruption of gap junction–mediated interaction between oligodendrocytes and astrocytes likely leads to an inability of these cells to regulate ion and fluid exchange, thereby contributing to the CNS phenotype [27, 31].

We would also like to comment that the commonly used term “encephalopathy” in the context of CMTX1 is probably a misnomer, because, to our knowledge, no convincing case, fulfilling strict diagnostic criteria for encephalopathy, has been described.

## Mild encephalitis/encephalopathy with a reversible splenial lesion

Mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) is a recently recognized subtype of acute encephalopathy [35]. Patients typically present with altered consciousness and/or delirious behavior, lasting for several days to weeks. The disturbance in mental status is thought to result from functional disconnection between cerebral hemispheres, whereas the prognosis is fairly good with complete resolution of the associated imaging abnormalities [35, 36].

The radiological hallmark of MERS, as its name implies, consists of lesions restricted to the splenium of the corpus callosum, which occasionally have the potential to expand to the nearby subcortical white matter, showing restricted diffusion on MR imaging [36, 37]. One hypothesis states that various conditions (viral infections, metabolic disorders, etc.) associated with uncontrolled cytokine and glutamate

release can cause disproportionate damage to the corpus callosum fibers, with the eventual development of cytotoxic, intramyelinic edema [37].

Interestingly, Kurahashi et al. provided preliminary evidence that genetic factors may contribute to this syndrome, at least in those cases where positive family history and relapsing/remitting course co-exist. They identified patients with familial MERS and extensive leukoencephalopathy, harboring mutations in the gene coding myelin regulator factor (MYRF), an essential component of oligodendrocyte differentiation and myelin maintenance [38]. Not surprisingly, MYRF and Cx32 possess similar biologic properties, acting in concert for the integrity of the myelin sheath [38]. This knowledge could possibly interpret the analogies between MERS and the CNS phenotype of CMTX1.

## Hemiplegic migraine

It has been demonstrated since the early 1980s that patients with hemiplegic migraine may suffer from impaired consciousness during their attacks [39–41]. Indeed, a recent nationwide Dutch study found confusion to be a regular accompaniment of the ordinary migraine paroxysms, especially in subjects carrying mutations in the three genes etiologically related to the familial type of hemiplegic migraine [42]. CACNA1A, encoding the pore-forming subunit of neuronal P/Q-type calcium channels; ATP1A2, responsible for the catalytic subunit of a glial and neuronal sodium-potassium pump; and SCN1A, encoding the pore forming subunit of neuronal Na<sub>v</sub>1.1 sodium channels, are ion transportation genes, critical for the maintenance of neuronal excitability and synaptic transmission [41]. Fever and seizures were also not uncommon in the above case series.

Earlier studies have estimated that debilitating attacks, unique to familial hemiplegic migraine, leading to profound coma of several days to weeks duration, may affect up to one-third of patients with CACNA1A mutation and 15% of ATP1A2 variants [43, 44]. Notably, major episodes of encephalopathy were extremely rare in the Danish population-based sample, which mainly included families lacking these mutations [45].

Clinical investigations frequently indicate CSF pleocytosis, cortical edema, and transient meningeal gadolinium enhancement, exclusively in cases of severe attacks, mimicking acute encephalitis. It is also clear that brain ischemia does not contribute to the phenotype.

The prognosis of the episodes is generally favorable, although fixed deficits or even death, exceptionally do occur. Minor head trauma, in analogy to VWM, appears to be a common precipitating factor of the attacks, whereas pregnancy and catheter angiography are similarly capable to uncover the genetic trait [40–43]. It is also of interest that a specific CACNA1A mutation (e.g., S218L) has the



particular potential to induce fulminant encephalopathy with early seizures and cerebral edema after trivial head injury [46]. Cellular and animal studies revealed that this dramatic phenotype is probably mediated by a pronounced effect of S218L on the threshold of cortical spreading depression initiation [47].

### Acute necrotizing encephalopathy

Acute necrotizing encephalopathy (ANE) is a rare and catastrophic type of encephalopathy affecting previously healthy children following a viral infection, such as influenza-A, herpes simplex virus, influenza-B, mycoplasma, and human herpes virus-6 [48]. Recently, SARS-CoV-2 has also been implicated [49]. ANE has a worldwide distribution with marked emphasis in the East [48]. According to Wu et al, who proposed diagnostic criteria for this disorder, patients demonstrate rapidly progressive consciousness alteration in association with convulsions and, sometimes, severe neurological deficits [50]. Clinical sequelae vary from complete recovery to death, whereas brain imaging reveals distinctive, but not pathognomonic, symmetric lesions in the basal ganglia, thalamus and brainstem, reminiscent of those seen in mitochondrial disorders, e.g. in Leigh syndrome [51, 52]. An interesting imaging feature that can further facilitate the recognition of ANE is the trilaminar sign of the thalamic lesions on DWI and ADC sequences, created by a multi-layered appearance of the underlying oedema and the presence of haemorrhagic foci [53].

The majority of cases are sporadic; however, case reports of familial occurrence with a tendency to recur, even in adulthood, led to the identification of the genetic subtype of this disorder, known as acute infection-induced encephalopathy 3, caused by a pathogenic dominant mutation in the RANBP2 (Ran Binding Protein 2) gene [51, 54]. In the genetic subtype, the MRI changes show a slightly different distribution in the external capsules, claustrum, limbic structures, and temporal lobes [52]. Interestingly, mutations in SCN1A, SCN2A, and RHOTB2 genes can similarly confer susceptibility to post viral necrotizing encephalopathy [55]. Further discussion of these conditions is beyond the scope of this review.

The postulated mechanisms of this fulminant encephalopathy, either of the genetic or acquired form, may relate to aberrant immunological response, although yet unclear [51]. Clinical neurologists should take ANE into account, whenever a major encephalopathy with compatible brain imaging develops after a viral respiratory prodrome. In the appropriate clinical setting, next-generation sequencing testing may potentially benefit the proband and his family members, offering the opportunity for preventative vaccinations and prompt intervention in the early stages of the illness.

### Hemophagocytic lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) is an uncommon, but frequently fatal, systemic inflammatory syndrome associated with diverse conditions, such as autoimmune, neoplastic, infectious or hereditary diseases [56]. It is thought that the common denominator of genetically determined and acquired HLH is a cytokine storm in the setting of defective natural killer/T cell function in the cytotoxic pathway having devastating consequences, such as end-organ failure and death if untreated [57]. The most commonly implicated genes in individuals with HLH are PRF1 and UNC13D, whereas a number of eponym immunodeficiency syndromes, e.g., Chediak-Higashi and Hermansky-Pudlak, have been linked to the development of HLH [57, 58].

Overall, CNS involvement has been reported in 30–75% of all HLH patients, either at presentation or during the course of the disease [58, 59]. Seizures and encephalopathy are the prevailing features followed by meningism and focal neurological signs. Valuable biologic markers favoring a diagnosis of HLH include peripheral cytopenias, hypertriglyceridemia, extreme elevation of ferritin, splenomegaly, and variable detection of hemophagocytes in blood or CSF. Neuroimaging depicts multifocal or confluent inflammatory lesions resembling ADEM, small vessel vasculitis, and CLIPPERS syndrome [58–60]. It is also intriguing the recent study of Benson et al. who reported on four patients with germline mutations in known HLH genes and exclusive CNS-restricted inflammation without involvement of the systemic compartment [60].

HLH can also be thought of as an endpoint of excess immune activation in the setting of systemic autoinflammatory disorders (SAIDs), which are mediated by dysregulation of the innate immune system [61]. Improvement in genetic tools has led to an increased identification of monogenic SAIDs in the adult population, like familial Mediterranean fever (FMF), cryopyrin-associated periodic syndromes (CAPS), and tumor necrosis factor receptor-associated periodic syndrome (TRAPS). Apart from their relation to HLH, autoinflammatory syndromes can have diverse neurological manifestations, mostly in the form of recurrent aseptic meningitis or meningoencephalitis, sensorineural hearing loss, and peripheral neuropathy [61].

HLH, including its genetic subtype, should be incorporated into the differential diagnosis of treatment refractory or recurrent CNS inflammation of uncertain etiology, since early detection and implementation of proper treatment (e.g., use of hematopoietic stem cell transplantation) may prevent irreversible neurological damage [60].

## Mitochondrial encephalopathies

Mitochondrial diseases arise as a result of mutations in either the mitochondrial genome per se or nuclear encoded genes involved in mitochondrial homeostasis and function [62]. Apart from a steady, progressive trajectory of peripheral and central nervous system dysfunction, a limited number of mitochondrial disorders may follow an acute or subacute course in the form of stroke-like episodes (SLEs) [63]. According to the recently published International Classification of Inherited Metabolic Disorders, mitochondrial diseases belong to their spectrum; despite this fact, we decided to include them to this review, because SLEs are not simply generated by the accumulation of an intermediate by-product of metabolism, but by the complex interplay of multiple heterogeneous factors, discussed below.

In a seminal paper, Hirano et al. defined SLEs as hallmarks of the syndrome of mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), generally caused by pathogenic variants in the mitochondrial gene MT-TL1 [64]. Besides MELAS, genetic variants in the nuclear POLG (polymerase gamma) gene, an essential component for the replication and repair of the mitochondrial DNA, have been consistently associated with acute encephalopathy. Using a large cohort of 155 patients with POLG-related disease in a multinational study, Hikmat et al. identified SLEs to be a common phenotypic feature in children and young adults below the age of 40 [65]. These cases, clinically indistinguishable from MELAS, may occur in the context of MEMSA (myoclonus, epilepsy, myopathy, and sensory ataxia) spectrum, formerly known as MSCAE (mitochondrial spinocerebellar ataxia with epilepsy) [65, 66]. Recently, a MELAS/Leigh overlap syndrome featuring SLEs due to mutations in the mtDNA genes MT-ND3 and MT-MD5 has been recognized, affecting exclusively young children [67].

Recently, a panel of experts provided consensus-based criteria of these acute events [68]. Briefly, they consist of abnormal level of consciousness ranging from lethargy to coma, focal, or generalized seizure activity, sometimes in the form of *epilepsia partialis continua* or overt status epilepticus, and focal motor deficits [66, 68, 69]. The episodes are commonly accompanied by migrainous features and severe cortical visual disturbances.

Apart from clinical similarities, SLEs in MELAS and MEMSA share several imaging and neuropathological findings. In particular, posterior brain regions (occipitotemporal in MELAS, mostly occipital in MSCAE) are especially vulnerable to the pathologic process, which manifests confluent edema in cortical and subcortical structures that span arterial territories [70]. In the majority of diffusion-weighted imaging studies, early cytotoxic edema is evident in the first few days of the attacks

gradually evolving to extracellular vasogenic edema, as cells undergo lysis and leak their contents [66, 71].

In the acute to subacute phase, brain MRI lesions closely resemble the defining abnormalities of posterior reversible encephalopathy syndrome (PRES) [72]. It appears that in the absence of the known predisposing conditions for PRES, neurological and radiological signs suggestive of PRES, warrant consideration of a possible underlying mitochondrial disorder [72]. Finally, the morphological equivalent of the episodes, known as stroke-like lesion (SLL), may either regress or expand reflecting the dynamic course of the pathobiological process [69, 71].

In regard to neuropathology, post-mortem studies of the affected cerebral tissue (SLL) have revealed sharply demarcated lesions with selective but incomplete neuronal loss, eosinophilic necrosis, and microglial activation, whereas microvascular network remains patent [66, 73, 74]. Cortical laminar necrosis is also observed, highlighting the role of energy failure in the pathogenesis [66, 73].

We underline that a similar phenotype of SLEs has also been rarely reported in the context of various other mitochondrial disorders caused by mutations of the mitochondrial or nuclear genome [75–79]. In sharp contrast to MELAS, the attacks do not belong to their fundamental manifestations [69, 71].

The pathophysiology of events underlying the development and progression of the SLLs is currently a matter of debate in the literature [80]. The prevailing, non-mutually exclusive, theories include metabolic disruption, vascular abnormalities, and epileptic factors [66, 68, 69, 71, 81]. It seems that the already metabolically challenged neurons by the respiratory chain dysfunction are vulnerable to the high energy demands posed by seizures, which result in further neuronal injury [66, 68]. This could provoke sustained ictal activity, perpetuating a vicious cycle that ends-up with a focal energy-dependent neuronal necrosis [68, 73]. In this regard, anti-epileptic prophylaxis has been recommended, at least for patients harboring POLG recessive mutations, who may suffer debilitating attacks [68].

Population studies from the UK and elsewhere have clarified that MELAS and POLG-related disease are not exotic causes of acute encephalopathy in the adult population [65, 82, 83]. Accordingly, neurologists could play a significant role in the establishment of a prompt diagnosis of mitochondrial disease. This might have important practical implications, not only from a prognostic perspective, but also in relation to therapeutic strategies (e.g., avoidance of sodium valproate in POLG disease, use of substances with potential benefit, and participation in clinical trials for novel therapies).

## Declarations

**Ethics approval** None.

**Conflict of interest** None.

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