
Neurological manifestations in autoinflammatory diseases

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ABSTRACT

Autoinflammatory diseases (AIDs) are a distinct group of diseases characterised by a dysregulation of the innate immune response leading to systemic inflammation. The clinical spectrum of these conditions is extremely variable and possibly every system and tissue can be involved, including the central nervous system (CNS). Indeed, neurological manifestations may dominate the clinical picture from disease onset in some rare conditions. However, the involvement of the CNS in AIDs is not a disease in itself, but represents a rare complication which is consequent to a systemic or local immune response, mainly involving cells of the innate immunity. This review will describe neurological manifestations associated with AIDs, including: chronic aseptic meningitis and brain atrophy, sensorineural hearing loss, early-onset haemorrhagic and ischaemic strokes, mental retardation, cerebellitis, and ataxia, and severe encephalopathy with brain calcifications.

Introduction

Autoinflammatory diseases (AIDs) are a distinct group of diseases characterised by a dysregulation of the innate immune response leading to a sterile multi-systemic inflammation (1, 2). The clinical spectrum of these conditions is extremely variable and possibly every system and tissue can be involved, including the central nervous system (CNS). In some rare conditions, neurological manifestations may dominate the clinical picture from disease onset. It is therefore necessary that paediatric and adult neurologists properly interpret clinical features that, in the context of systemic inflammation, should lead to the suspicion of an inherited AID.

Role of the innate immunity in CNS inflammation

In general, the innate immune system responds rapidly, in a non-specific manner, to stimuli that are perceived

as harmful. Such stimuli could include invading pathogens, cancer cells or tissue damage. Within the CNS, cells of the innate immunity are mainly non-parenchymal meningeal, perivascular, and choroid-plexus macrophages, and a unique myeloid cell population of tissue-resident parenchymal macrophages, called microglia (3). Microglia are involved in the maintenance of CNS homeostasis controlling synaptic density, connectivity and plasticity, clearing myelin debris and apoptotic cells, and influencing sprouting, migration, anastomosis, and refinement of the growing CNS vasculature. Microglia also release pro-regenerative factors during CNS development and, to a lesser extent, following tissue injury during adult life. In addition, microglia continuously patrol the CNS microenvironment interacting dynamically with surrounding cells and seeking for molecular signatures characteristic of pathogens and tissue injury. Upon sensing changes through cell surface receptors, such as the Toll Like Receptors and others, microglia become activated undergoing morphological and functional changes leading to secretion of cytokines and chemokines, including tumour necrosis factor- α , interleukin (IL)-6, IL-1 β , IL-12, and CC chemokine ligand (CCL)-2, phagocytosis and, on occasion, direct cytotoxicity (4). In addition, non-parenchymal CNS macrophages have been shown to act as antigen-presenting cells, perform phagocytosis, and respond to CNS inflammation, neurodegeneration, and peripheral inflammation. After tissue injury, a second population of monocyte-derived macrophages infiltrate the CNS from the periphery, acquiring, similar to microglia, a detrimental or beneficial phenotype depending on the microenvironment. However, systemic inflammation also leads to activation of microglia and migration of blood-borne innate cells; these are mainly macrophages but also include neutrophils, sparse mast cells, dendritic cells,

and natural killer cells, through a leaky blood brain barrier.

Early activation of microglia and infiltrating macrophages is a prompt response to danger signals, which attempts to limit inflammation and promote tissue repair. The sustained activation of microglia and infiltrating macrophages, often triggered by pro-inflammatory cytokines, reactive oxygen species, misfolded proteins, and toxic factors, results in the acquisition of a detrimental phenotype by releasing inflammatory mediators that promote protein aggregation and neuronal damage. This leads to further migration of immune cells in the CNS and the involvement and activation of astrocytes. Astrocytes are glial cells of neuroepithelial origin with sophisticated functions including buffering CNS potassium, removing and recycling potentially toxic glutamate, adjusting water balance, and modulating synaptic activity and blood flow. Astrocytes also produce neurotrophins and anti-inflammatory cytokines, but they can also release inflammatory mediators, including several complement components, IL-1 β , IL-6, and chemokines.

Neurological manifestations associated with AIDs

Chronic aseptic meningitis and brain atrophy

Cryopyrin-associated periodic syndromes (CAPS) are a group of clinical conditions (Familial cold autoinflammatory syndrome [FCAS]; Muckle-Wells syndrome [MWS]; and chronic infantile neurological cutaneous articular syndrome [CINCA]) independently identified and associated with autosomal dominant or *de novo* mutations of the *NLRP3* gene (Table I) (5). These inflammatory conditions have in common a number of clinical manifestations, including, urticarial-like skin rash, arthralgia/arthritis, and conjunctivitis (6). *NLRP3* (also called cryopyrin) is a member of the NOD-like receptor (NLR) protein family and a key protein of the inflammasome (7). Following its activation by a number of pathogen- or damage-associated molecular patterns (PAMPS or DAMPS), *NLRP3* oligomerises and binds the adaptor pro-

tein apoptosis-associated Speck-like protein containing a CARD (ASC). This association directly activates two molecules of caspase-1, which in turn converts pro-IL-1 β to the mature, active 17 kDa form (7). Gain-of-function mutations of cryopyrin lead to a multi-systemic inflammatory condition with a wide phenotypical spectrum according to the severity of *NLRP3* mutations (8, 9).

The most severe clinical form of CAPS, namely CINCA, which is also known as neonatal onset multi-systemic inflammatory disease, was originally identified in 1981 by Prieur and Griselli (10). This study described three unrelated children who presented since birth with an inflammatory syndrome characterised by a permanent skin rash, fever, lymphadenopathy, and a severe involvement of the CNS (10). CINCA patients display a typical “facies”, featured by frontal bossing, large cephalic perimeter, and saddle-back nose (Fig. 1) (11). If untreated, these patients develop permanent organ damage as a consequence of chronic CNS inflammation. Chronic aseptic meningitis, possibly consequent to the activation of non-parenchymal myeloid cells, leads to increased intracranial pressure resulting in hydrocephalus, brain atrophy, and chronic papilledema (Fig. 1). Neurological symptoms typical of CINCA are characterised by chronic irritability, mental retardation, headache, early morning nausea, vomiting, and rarely, seizures (12). Notably, 8 of 18 (44%) CINCA patients (aged 4–32 years) with active disease displayed an extremely low or borderline cognitive function at baseline (13).

Persistent papilledema is also common and, if not treated, may cause optic nerve atrophy with progressive vision loss (11). Chronic cochlear inflammation leads to a progressive and severe hearing loss in the first years of life (see below) (11).

Sub-chronic or chronic headache and a more delayed and progressive sensorineural hearing loss can also be observed in MWS, an intermediate and less dramatic subtype of CAPS (12, 14).

As stated above, CAPS is usually transmitted in an autosomal dominant fash-

ion (5). The search for other affected family members is therefore extremely important, especially in patients with a milder phenotype, such as MWS. Conversely, patients with the most severe CINCA phenotype are usually carriers of *de novo* *NLRP3* mutations, and the family history can be negative. Finally, a substantial percentage (up to 30%) of patients with a clinical picture suggestive of CINCA can result to be negative for germinal mutations of *NLRP3*, but are carriers of a somatic mosaicism of the gene that should be systematically searched for in patients with a consistent phenotype (15). The prompt diagnosis of a severe CINCA phenotype is crucial for the timely introduction of a proper treatment that, if started in the first months of life, can prevent the development of chronic aseptic meningitis, brain atrophy, and mental retardation (16).

Sensorineural hearing loss

As anticipated above, persistent cochlear inflammation leads to sensorineural hearing loss in almost all CINCA patients before the age of 5 years and in a relevant percentage of patients with MWS or FCAS in adulthood (12, 17). In untreated CINCA patients with a long disease course, 83% of the patients displayed a certain degree of hearing loss; for >50% of patients, moderate-to-severe hearing loss was recorded (11). Similarly, hearing loss was observed in 60% of patients in an Italian study of CAPS patients with a long disease history (18).

A prospective study, which evaluated audiological parameters of 57 CAPS patients (31 patients with CINCA) and for which complete audiological data were obtained for 70% of ears, showed conductive hearing loss in 11% of ears, a mixed hearing loss in 13%, and a sensorineural hearing loss in 61% of CINCA ears (17). Sensorineural hearing loss in CINCA is characteristically worst at higher frequencies. Cochlear enhancement on fluid attenuation inversion recovery (FLAIR)-magnetic resonance imaging (MRI) sequences of the brain and inner ear was observed in 90% (26/29) of patients with CINCA, hence cochlear enhancement appears

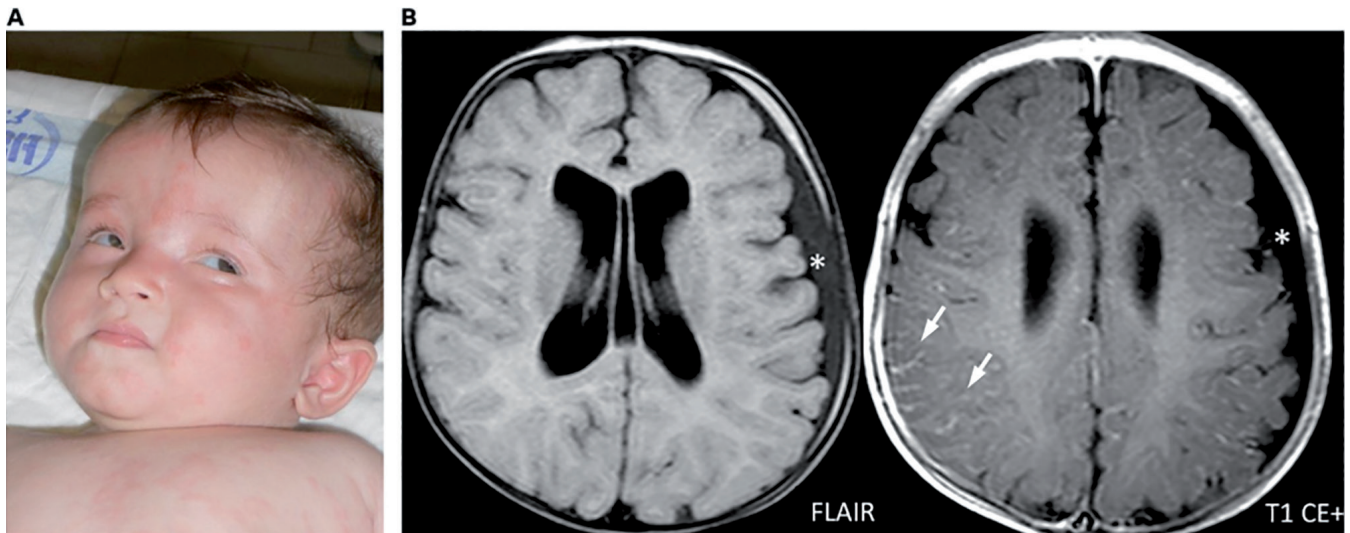


Fig. 1. (A) Clinical presentation of a 7-month old patient with chronic infantile neurological cutaneous articular (CINCA) syndrome showing a severe neurological involvement. (B) Magnetic resonance imaging in the same CINCA patient shows bilateral subdural fluid collections (asterisk) and mild leptomeningeal contrast enhancement (arrows) at right parietal lobe (courtesy of Dr M.S. Severino).

to be an accurate predictor of cochlear hearing loss (17).

Biologic treatment has shown a beneficial effect on hearing loss, with a decrease in or disappearance of cochlear enhancement reported in 13 of 17 (76%) CINCA patients after three months' therapy (13). More recently, it has been observed that, despite optimal treatment, almost 20% of ears of CINCA patients evolved to hearing loss (17).

Despite the use of a suitable biologic treatment, residual inflammatory activity has been detected in the cerebral fluid of CINCA patients with complete control of other systemic manifestations (19). This issue could reflect the limited capability of the different drugs (especially monoclonal antibodies) to cross the blood brain barrier (20). Moreover, recent data highlight the possibility of a different pattern of CNS inflammation in CINCA patients, with a major role for IL-6 and IP-10 that have been postulated to be produced locally by the microglia (21).

Early-onset haemorrhagic and ischaemic strokes

Deficiency of adenosine deaminase 2 (DADA2) is a recently identified AID characterised by multi-systemic, inflammatory vasculopathy (Table I; Fig. 2) (22, 23). DADA2 is mainly characterised by chronic or recurrent

systemic inflammation with fever and elevation of acute phase reactants, usually associated with cutaneous features clinically and histologically consistent with a polyarteritis nodosa (PAN). Skin manifestations range from livedo racemosa to maculopapular rash, nodules, ulcerative lesions, and digital necrosis (22, 23). In the majority of patients, a severe neurological involvement, affecting both the peripheral and CNS, has been described. Many patients develop ischaemic or haemorrhagic strokes very early in childhood. In some cases, cerebral haemorrhage can occur. DADA2-associated strokes are typically lacunar and are associated with different manifestations ranging from severe and permanent disability to clinically silent ischaemic or haemorrhagic episodes (22, 23). In some patients, transitory ischaemic attacks can occur, with negative cerebral computed tomography (CT) and/or MRI (22, 23). Similar to multifactorial PAN, DADA2 patients can also present a peripheral neuropathy ranging from transient mononeuritis, such as a cranial nerve transient paralysis, to permanent polyneuropathy. Few patients may develop optic neuritis (22-26). Recently, the occurrence of acute hearing loss, likely associated to an ischaemic event, has also been observed in a cohort of Italian patients affected with ADA2 deficiency (27).

DADA2 is secondary to loss-of-function mutations of the *CECR1* gene, coding for deaminase 2 (22, 23). ADA2 shows a homology with the ADA1 protein, which is associated with a form of severe combined immunodeficiency (24). Both these deaminase adenosine proteins play a crucial role in the regulation of the purinergic signalling pathway by converting adenosine to inosine and 2'-deoxyadenosine to 2'-deoxyinosine, respectively (28). In contrast to ADA1, which is present in all cell types, ADA2 is mostly expressed in monocytes and cells of myeloid lineage (28). ADA2 also acts as a growth-factor and plays a pivotal role in the development of haematopoietic and endothelial cells (28). Finally, ADA2 also has an autocrine activity and is able to induce monocyte proliferation and macrophage differentiation (29). Recent data show that ADA2-deficient patients display some impairment of B cell functions, a defect in the differentiation to anti-inflammatory (M2) macrophages, with a consequent prevalence of pro-inflammatory (M1) cells and inflammatory abnormalities in brain endothelial cells (23).

DADA2 is usually transmitted as a recessive autosomal disorder (22, 23). Thus, the presence of a parental consanguinity or the identification of a possible endogamy should be considered as a relevant indication for ge-

Table I. Monogenic autoinflammatory diseases associated with severe neurological manifestations.

Disease	Gene/Protein	Inheritance	Main Clinical Manifestations	Disease Mechanisms
CAPS	<i>NLRP3/NLRP3</i>	AD	FCAS: rash, fever and arthralgia after cold exposure. MWS: recurrent or sub-chronic urticarial rash, arthralgia, sensorineural hearing loss. CINCA: as for MWS plus mental retardation, chronic aseptic meningitis and bone deformities.	- Gain-of-function mutations with sustained NLRP3 activation and IL-1 β release. - Redox homeostasis perturbation and cell stress leading to increased ATP production and defective secretion of IL-1 receptor antagonist.
MKD	<i>MVK/MK</i>	AR	Mevalonic aciduria: dysmorphic features (microcephaly, dolichocephaly, low set ears, wide fontanelle), neurologic symptoms (hypotonia, developmental delay, ataxia associated with cerebellar atrophy), cataracts, failure to thrive. Hyper IgD. Early onset (<24 months). Fever episodes (4–5 days) with abdominal pain, vomiting, diarrhoea, and splenomegaly. Late onset ataxia, mild mental retardation, and epilepsy in rare adult cases.	- Loss of function: shortage of non-sterol isoprenoid products. - Impaired protein prenylation causing ER stress-driven UPR initiation and defective autophagy. - Activation of Pyrin Inflammasome and IL-1 β over-secretion.
DADA2	<i>CECR1/ADA2</i>	AR	Recurrent fever, livedoid rash and early onset polyarteritis-like vasculopathy, hypogammaglobulinemia. Ischemic and haemorrhagic strokes, acute hearing loss.	- Loss of function: impaired differentiation of M2 macrophage. - Impaired growth factor activity on hematopoietic and endothelial cells.
Aicardi-Goutieres	<i>Ifih1/IFIH1</i> <i>Trex1/TREX1</i> <i>Adar/ADAR1</i> <i>Ags5/SAMHD1</i> <i>Rnaseh2a/RNASEH2A</i> <i>Rnaseh2b/RNASEH2B</i> <i>Rnaseh2c/RNASEH2C</i>	AD AR AR AR AR AR AR	Progressive encephalopathy, with acquired microcephaly, cerebral atrophy, intracranial calcifications, leukodystrophy. SLE-like manifestations: chilblains, thrombocytopenia, serum autoantibodies.	- Proteins involved in clearing the cellular nuclear acid “debris”. - Loss of function: immune activation normally induced by viral nucleic acid. - Type-I over-secretion.

AD: autosomal dominant; AR: autosomal recessive; ATP: adenosine triphosphate; CAPS: cryopyrin-associated periodic syndromes; CINCA: chronic infantile neurological cutaneous and articular syndrome; DADA2: adenosine deaminase 2 deficiency; ER: endoplasmic reticulum; FCAS: familiar cold autoinflammatory syndrome; IL: interleukin; MWS: Muckle–Wells syndrome; MKD: mevalonate kinase deficiency; SLE: systemic lupus erythematosus; UPR: unfolded protein response.

netic testing in patients with a DADA2 phenotype. In any case, molecular testing of the *CECR1* gene should be performed in all individuals presenting in childhood with ischaemic or haemorrhagic strokes or with a positive history for PAN-like clinical manifestations.

Mental retardation, cerebellitis, and ataxia

Mental retardation is a common clinical feature of many inherited metabolic conditions secondary to enzymatic defects that may present in early infancy. In some of these conditions a severe chronic or recurrent inflammatory condition can be associated. This is the case for an inborn error of cholesterol biosynthesis caused by mevalonate kinase (MVK) deficiency (Table I) (30). This enzyme is located at the beginning of the cholesterol biosynthesis

pathway compromising the biosynthesis of nonsterol isoprenes in addition to cholesterol (30). Homozygous or biallelic heterozygous mutations of the *MVK* gene lead to an impaired enzymatic activity, with differing degrees of severity. The almost complete deficiency of the enzymatic activity of *MVK* is associated with a severe multi-systemic disease known as Mevalonic Aciduria (MA), which is characterised by dysmorphic features (microcephaly, dolichocephaly, low set ears, wide fontanelle), neurologic symptoms (hypotonia, developmental delay, ataxia associated with cerebellar atrophy), cataracts, and failure to thrive (30, 31). Mild-to-severe mental psychomotor retardation is frequently observed. In the milder cases, during the scholar age, ataxia due to progressive cerebral atrophy become the predominant finding, associ-

ated with ocular involvement (uveitis, cataracts and tapetoretinal degeneration). Besides these severe manifestations, patients also display recurrent flares of inflammation associated with fever, abdominal pain with enteropathy, hepatosplenomegaly, lymphadenopathy, arthralgia, and morbilliform rashes (30, 31).

The milder form of the *MVK* deficiency (MKD), also known as Hyper IgD syndrome (HIDS), is the result of a partial enzymatic effect of *MVK* secondary to milder variants of *MVK* genes, such as V377I (32). These children do not present the dysmorphic features and severe neurological manifestations of MA. Their disease is essentially dominated by recurrent fever episodes lasting 4–6 days and associated with the same clinical features described above for MA, namely abdominal pain, diar-

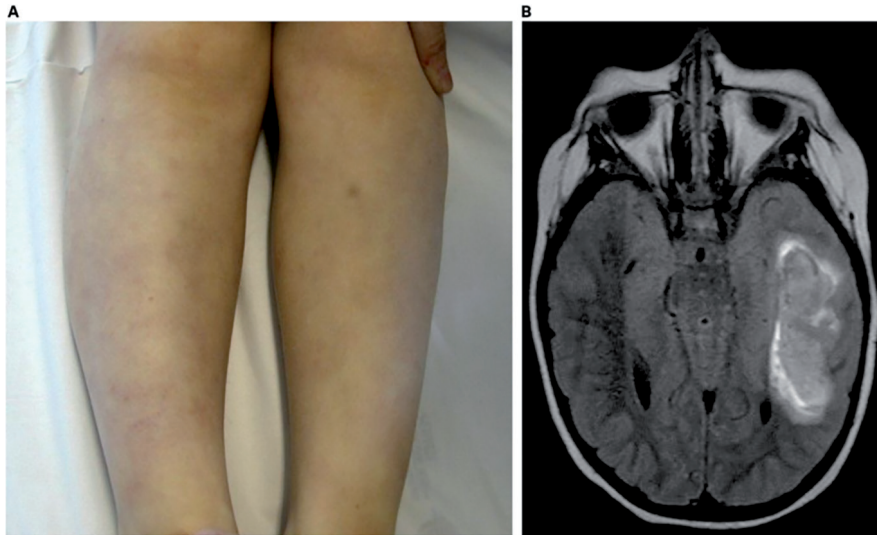


Fig. 2. (A) Livedo reticularis in a deficiency of adenosine deaminase 2 (DADA2) patient. (B) Large haemorrhagic stroke in a 5-year old patient with DADA2.

rhoea, vomiting, arthralgia, skin rash, lymph node enlargement, and splenomegaly (33, 34).

Interestingly, a group of adult HIDS patients developed neurological abnormalities (ataxia, mental retardation, epilepsy) together with MA-associated ocular manifestations reflecting the existence of a continuum between MA and HIDS (33).

Patients with MKD present with an increased excretion of mevalonic acid in the urine, especially during the febrile crisis (35). For many years, hyperimmunoglobulinemia D was considered a hallmark of the disease. However, it is now clear that elevation of IgD can be found in other periodic syndromes and can be absent in MKD patients (36). The confirmatory diagnosis of MKD relies on the molecular analysis of MVK and on the identification of two bi-allelic variants.

Severe encephalopathy with brain calcifications

Another inflammatory condition, presenting with severe neurological manifestations, is Aicardi-Goutieres syndrome (AGS) (Table I) (37). AGS is a progressive encephalopathy characterised by acquired microcephaly, cerebral atrophy, intracranial calcifications, and leukodystrophy. In almost 20% of patients, the disease has a neonatal onset (38). Patients present with jitteriness, poor feeding, and seizures.

They also exhibit poor head control, trunk hypotonia, persistence of archaic reflexes, and dystonic movements. Microcephaly and cerebral calcifications can be detected in utero, reflecting the prenatal onset of the disease (37). The presentation resembles that caused by transplacental-acquired infections and originally it was referred to as pseudo-TORCH (toxoplasma, rubella, cytomegalovirus and Herpes simplex). However, the lack of hearing loss and retinal abnormalities are useful differentiating features from congenital infections (37). In other patients, disease onset is usually at the age of 4 months after an initial normal development. Patients present with irritability, disturbed sleeping pattern, and feeding difficulties. Medium-grade fever is often present, leading to an erroneous suspicion of encephalitis. Analysis of cerebrospinal fluid (CSF) typically reveals lymphocytosis ($>5\text{--}100$ cells/ mm^3) and elevated interferon (IFN)- α levels in the absence of signs of infection (38). Cerebral calcifications in the basal ganglia and in the deep white matter, cerebral atrophy, and white matter abnormalities consistent with leukodystrophic patterns are commonly detected by brain CT scan and MRI (37, 38). Patients progress towards a progressive encephalopathy with psychomotor delay and/or loss of acquired skills. This encephalitic phase lasts for a few months, followed by a subse-

quent stabilisation of the neurological picture, with severe residual permanent damage.

Beyond the neurological phenotype, patients develop a number of autoimmune systemic lupus erythematosus (SLE)-like manifestations such as chilblains, thrombocytopenia, and positive serum autoantibodies over time (37). As suggested by CSF findings, type I IFN play a critical role in disease pathogenesis and almost all patients present a strong IFN signature in the peripheral blood (39). Newborn mice injected with type I IFN presented the same manifestations (growth retardation, liver lesions, glomerulonephritis) observed in animals infected by lymphocytic choriomeningitis virus (LCMV), suggesting that type I IFN itself is responsible for the induction of these lesions (39).

A number of genes are associated with AGS and include, *TREX1* (AGS1), *SAMHD1* (AGS5), *RNaseH2A* (AGS4), *RNASEH2B* (AGS2), *RNASEH2C* (AGS3), *ADARI* (AGS6), and *IFIH1* (AGS7) (37). Interestingly, all mutations described so far in AGS are involved in the metabolism of nucleic acids or their recognition machinery, i.e. the receptors that are responsible for sensing pathogen-derived nucleic acids and the related downstream mediators. An increase in the burden of nucleic acids derived from endogenous retroelement or by the constitutive activation of nucleic acid receptors and mediators leads to an over-activation of the type I IFN pathway, which is probably responsible for the neurological damage and SLE-like autoimmune phenomena observed in AGS. Indeed, a large amount of evidence supports the pivotal role of type I IFN in the pathogenesis of SLE (40, 41). Interestingly, rare cases of monogenic forms of SLE have been reported in patients harbouring mutations observed in AGS, including *TREX1*, *SAMHD1*, and *ACP5* (37, 42). These findings support the current concept that AGS belongs to the new class of type I interferonopathies, a clinically heterogenic group of Mendelian diseases with a constitutive activation of type I IFN pathway (43). This group also includes monogenic forms

of SLE and other severe multi-systemic inflammatory conditions such as Proteasome Associated Autoinflammatory Syndromes (PRAAS) and stimulator of IFN genes (STING)-associated vasculopathy with onset in infancy (SAVI) (44, 45).

Conclusions

CNS involvement in AIDs is not a disease in itself, but represents a rare complication consequent to systemic or local immune response, mainly involving cells of the innate immunity. The heterogeneity of neurological symptoms is likely due to the complexity of the pathobiology of different diseases targeting parenchymal and non-parenchymal myeloid cells, whose anatomical distribution may explain the different clinical manifestations. For example, wide-spread activation of meningeal, perivascular, and choroid-plexus macrophages may be the driving force of increased intracranial pressure with subsequent hydrocephalus, headache, nausea, vomiting, and seizures, which are common neurological symptoms of CAPS. Regardless of the poor nosographic definition of neurological diseases, particularly in infants and paediatric patients, the occurrence of neurological symptoms in patients with AIDs should warn clinicians to perform CSF analysis and brain MRI at the earliest opportunity and to begin appropriate treatment without delay to avoid irreversible neurological complications.

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