



Rare genetic causes of meningitis and encephalitis

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Differential diagnosis of meningitis and encephalitis is often very challenging because it cannot be determined based on symptoms, and the diseases have various causes. This article explains rare genetic causes of meningitis and encephalitis. Autoinflammatory disorders include cryopyrin-associated periodic syndromes, familial Mediterranean fever, and tumor necrosis factor receptor-associated periodic syndrome. Furthermore, other genetic disorders, such as complement factor I deficiency, phosphatidylinositol glycan anchor biosynthesis class T mutation, and neuronal intranuclear inclusion disease, can present as meningitis and encephalitis.

Keywords: Rare diseases, Inborn genetic diseases, Meningitis, Encephalitis, Differential diagnosis

Introduction

Diagnosis and management of meningitis and encephalitis are challenging for clinicians because of the variety of causes [1]. Over the past decade, autoimmune encephalitis (AE) has become more recognized, and its reported incidence has increased. AE can be diagnosed based on clinical diagnostic criteria regardless of the presence of autoantibodies [2,3]. The existence of autoantibodies should not be a prerequisite for AE diagnosis because not all disease-causing antibodies have been identified, with novel antibodies discovered in AE patients every year [4–6]. Due to the increased awareness of AE and its potential responsiveness to immunotherapy, antibody-negative AE currently occupies a substantial portion of AE. Though immunotherapy is performed in patients with antibody-negative AE, the response varies [7–9]. In suspected AE cases with insufficient treatment response, the possibility of other diagnoses should be considered.

In recent years, genetic diagnosis of rare diseases has been increasing due to advances in sequencing technology [10,11]. Consequently, rare genetic diseases that occur in the form of meningitis or encephalitis have been discovered. This study

summarizes the types of rare genetic diseases that should be considered as differential diagnosis of meningitis and encephalitis (Table 1).

Autoinflammatory disorders

Autoinflammatory disorders (AIDs) are systemic disorders of innate immunity without the presence of antibodies or reactive T cells [12]. AIDs usually manifest during childhood and are characterized by repeated episodes of inflammation; however, adult-onset cases have been reported [13]. Aseptic meningitis can be an initial manifestation of AIDs, complicating its distinction from autoimmune or infectious diseases [14]. Subtypes of AIDs that can present as aseptic meningitis are discussed in the following section (Table 1).

Cryopyrin-associated periodic syndromes: NLRP3 mutation

Cryopyrin-associated periodic syndromes (CAPS) are a group of autosomal dominant hereditary systemic autoinflammatory diseases that include mild subtype familial cold-induced

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Table 1 Summary of monogenic disorders that can cause meningitis and encephalitis

Disease	Gene	Inheritance	Age of onset (yr)	Neurological symptom	Systemic symptom
CAPS	<i>NLRP3/CIAS1</i>	AD	Variable	Aseptic meningitis	Fever, urticaria-like rash, conjunctivitis, arthralgia, sensorineural hearing loss
FMF	<i>MEFV</i>	AR/AD ^a	0–30	Aseptic meningitis	Fever, rash, serositis, arthritis (in large joints)
TRAPS	<i>TNFRSF1A</i>	AD	Variable	Aseptic meningitis	Fever, migrating skin rash, serositis, periorbital edema, arthritis
CFI deficiency	<i>CFI</i>	AR	0–60	Aseptic meningitis, hemorrhagic leukoencephalitis	Severe recurrent infections, glomerulonephritis, pneumonia, arthritis
PIGT mutation	<i>PIGT</i>	AR	Variable (neonatal–adult)	Aseptic meningitis, neonatal seizure, intellectual disability	Fever, paroxysmal nocturnal hemoglobinuria, urticaria, arthralgia
NIID	<i>NOTCH2NLC</i>	AD	Variable (< 40)	Dementia, cerebellar ataxia, parkinsonism, peripheral neuropathy, seizure, pupil constriction	Chronic cough, paroxysmal chest pain, postural hypotension, muscle weakness, joint pain, urinary frequency/urgency, constipation

CAPS, cryopyrin-associated periodic syndromes; FMF, familial Mediterranean fever; TRAPS, tumor necrosis factor receptor-associated periodic syndrome; CFI, complement factor I; PIGT, phosphatidylinositol glycan anchor biosynthesis class T; NIID, neuronal intranuclear inclusion disease; AD, autosomal dominant; AR, autosomal recessive.

^aFMF is classically known as AR disease; however, rare cases of AD FMF with specific heterozygous mutations have been reported.

autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and chronic infantile neurological, cutaneous, and articular syndrome (CINCA; also called neonatal-onset multisystem inflammatory disease), which is the most severe subtype [15,16]. The syndromes are all caused by heterozygous gain-of-function mutation in the *NLRP3* gene (also known as *CIAS1*, *NALP3*, or *PYPAFI*) that encodes the protein cryopyrin, a component of the *NLRP3* inflammasome. This mutation leads to hyperactivation of the inflammasome and subsequent overproduction of proinflammatory cytokine interleukin (IL)-1 β and inflammatory symptoms. The diagnosis of CAPS is challenging due to the heterogeneous multisystemic clinical presentation, somatic mosaicism, and low-penetrance mutations [16,17].

Historically, FCAS, MWS, and CINCA have been accepted as three distinct diseases but are now considered a single disease spectrum with overlapping signs and symptoms. CAPS are multisystem inflammatory diseases that affect skin, muscles, joints, bones, eyes, ears, and the central nervous system (CNS) [16]. CNS involvement is the most devastating feature of CAPS. Although patients with MWS rarely have intermittent aseptic meningitis, patients with CINCA often develop recurrent chronic aseptic meningitis leading to increased intracranial pressure, hydrocephalus, papilledema, headache, and seizures [15].

Other typical signs and symptoms of CAPS include dermatological (urticarial-like rash), musculoskeletal (arthralgia, arthritis, myalgia, limb-length discrepancies and contractures, clubbing, patellar overgrowth), ocular (conjunctivitis, uveitis, papilledema, progressive amaurosis), and inner ear (sensori-

neural hearing loss) manifestations [18]. However, fever is not a common presenting symptom in patients with CAPS, and body temperature does not meet the standard criteria for fever [16].

By 2018, more than 90 confirmed disease-causing mutations in *NLRP3* have been reported. More than 90% of these mutations are located in exon 3, which encodes the central regulatory domain of the protein and is reported to show good genotype-phenotype correlation, indicating that each mutation is likely associated with only one clinical phenotype among the disease continuum. Up to 50% of patients with CINCA, 25% of patients with MWS, and 10% of patients with FCAS do not have a germline *NLRP3* mutation [19], and the majority of these patients have somatic mosaicism in *NLRP3* [16]. Low-penetrance mutations have been reported in CAPS, indicating that only a small portion of subjects carrying the mutation will develop symptoms. In particular, V198M, R488K, and Q703K variants have been described in up to 10% of the normal population [16,20].

Diagnosis of CAPS can be made clinically and genetically but is often delayed. Low awareness of CAPS among physicians and cases with somatic mutations are the main cause of delay in diagnosis. Although early onset of symptoms is a strong indicator for CAPS, some patients show only mild symptoms, indicating the importance of consideration of CAPS in adults [21]. Clinical diagnostic criteria for CAPS have been recently developed [22]. Increased inflammatory markers are a mandatory criterion, and more than two of six additional items are required for diagnosis (Figure 1). The presence of *NLRP3* mutations can be confirmatory although not necessary for diag-

Figure 1 Diagnostic criteria for CAPS

Mandatory criteria
<ul style="list-style-type: none"> • Increase inflammatory markers (C-reactive protein and/or serum amyloid A)
Additional criteria (≥ 2 of 6 CAPS typical signs/symptoms)
<ul style="list-style-type: none"> • Urticaria-like rash • Cold/stress-triggered episodes • Sensorineural hearing loss • Musculoskeletal symptoms (arthralgia/arthritis/myalgia) • Chronic aseptic meningitis • Skeletal abnormalities (epiphyseal overgrowth/frontal bossing)

CAPS, cryopyrin-associated periodic syndromes.

nosis of CAPS; thus, a genetic diagnosis is required before initiation of appropriate therapy.

Despite clinical heterogeneity, patients with CAPS respond well to IL-1 blockade treatment. To date, three IL-1 blockade therapies, anakinra (Kineret; Sobi, Stockholm, Sweden), rilonacept (Arcalyst; Regeneron, New York, NY, USA), and canakinumab (Ilaris; Novartis, Basel, Switzerland), have been approved by the Food and Drug Administration or European Medicines Agency for treatment of CAPS [16].

Familial Mediterranean fever

Familial Mediterranean fever (FMF) is the most common monogenic cause of AID and is characterized by recurrent fever and multiple serositis. FMF is an autosomal recessive disorder caused by mutations in the *MEFV* gene, which encodes the protein pyrin. Pyrin negatively regulates the activation of inflammasomes through regulation of IL-1 β production [23]. Pyrin mutations lead to increased synthesis of proinflammatory cytokines (IL-1 β and IL-6) and cause changes in inflammasome function. Although FMF is typically inherited in an autosomal recessive manner, dominant inheritance with specific heterozygous mutations has been reported [24].

Disease onset occurs before 10 years of age in more than 60% of patients and before 30 years of age in 98% of cases [25]. Adult-onset patients often have milder phenotype and can present with uncommon manifestations such as aseptic meningitis. Aseptic meningitis in FMF follows a similar pattern, with typical symptoms including self-limiting episodes lasting 3 to 5 days. However, according to previous reports, aseptic meningitis is a very rare manifestation of FMF. In one study, only seven of 12,000 adult patients with FMF between 1985 and 2010 experienced aseptic meningitis without a clear de-

scription of recurrent attacks [26]. During the last 10 years, five cases of recurrent aseptic meningitis have been reported [27]. The age of onset ranged from 5 to 46 years, and every patient responded to colchicine treatment. Notably, all five patients carried the E148Q variant in exon 2 as homozygote or heterozygote accompanied by another variant. None of the patients had a pathogenic variant in exon 10.

To date, more than 370 *MEFV* nucleotide variants have been reported. Among them, five variants, M694V, M694I, V726A, and M680I in exon 10, and E148Q in exon 2, are responsible for approximately 85% of cases [28]. The majority of FMF-causing mutations are located in *MEFV* exon 10 and associated with the typical and severe phenotype of recurrent inflammatory episodes. The typical FMF phenotype includes periodic fever and abdominal or chest pain lasting for a few hours to 3 days. Notably, M694del has been reportedly associated with autosomal dominantly inherited FMF [24,29].

In terms of treatment, colchicine is considered the gold standard for FMF patients. When colchicine treatment is ineffective, other biologics such as IL-1 inhibitors and tumor necrosis factor (TNF)- α blockers can be used. Examples include anakinra, canakinumab, and rilonacept as IL-1 inhibitors and infliximab and etanercept as TNF- α blockers [30].

Tumor necrosis factor receptor-associated periodic syndrome

TNF receptor-associated periodic syndrome (TRAPS) is an autosomal dominant disorder caused by mutation in the *TNFRSF1A* gene that encodes TNF-receptor 1. Among the monogenic AIDs, TRAPS shows the most variable manifestation in terms of age of onset, disease duration, and clinical presentation. The pathogenesis of TRAPS is complex and involves multiple mechanisms including increased endoplasmic reticulum stress, excessive mitochondrial reactive oxygen species, and enhanced nuclear factor kappa B (NF- κ B) activation [31].

Most TRAPS patients experience early-onset symptoms, but adult-onset TRAPS has been widely reported, especially in subjects carrying low-penetrance mutations and presenting an atypical phenotype. Fever and serositis presenting as migratory skin rash, myalgia, abdominal pain, and periorbital edema are the most common clinical features [31]. Aseptic meningitis is considered an atypical symptom of TRAPS, and CNS involvement has been reported in a limited number of cases [32,33].

To date, no clinical diagnostic criteria of TRAPS have been proposed; thus, diagnosis of TRAPS is based on identification of *TNFRSF1A* mutation. All TRAPS pathogenic variants are clustered in exons 2–4; however, R92Q and P46L are considered low-penetrance variants [31].

Corticosteroids are very effective for treatment of TRAPS, but chronic use is limited due to their long-term toxicity. IL-1 blocking agents are suggested as treatment of choice for the majority of patients with active TRAPS [31].

Other genetic disorders

In addition to the above-mentioned AIDs, several other monogenic diseases resemble meningitis and encephalitis. Therefore, although very rare, the possibility of the following genetic disorders in patients with meningitis and encephalitis should be considered.

Complement factor I deficiency

Defect in homeostasis of the complement system can result in autoimmune reactions with variable clinical presentations. Complement factor I (CFI) is a serine protease with an important regulatory role in the alternative complement pathway. CFI deficiency, a rare autosomal recessive disorder, is associated with recurrent infections as well as relapsing inflammatory responses.

Haerynck et al. [34] reported a case of a 16-year-old female with CFI deficiency who experienced recurrent episodes of acute aseptic meningoencephalitis. Ten episodes of meningoencephalitis occurred over a 15-month period. Corticosteroid treatment and plasmapheresis were effective, but she relapsed several times after tapering steroids. Cyclophosphamide and azathioprine were administered to reduce the daily dose of steroids, severe relapses prompted a change to mycophenolate mofetil, and no further relapse occurred.

Broderick et al. [35] described two unrelated pediatric patients with acute hemorrhagic leukoencephalitis caused by CFI deficiency. Both patients showed extensive white matter signal abnormalities on magnetic resonance imaging (MRI), and brain biopsy revealed neutrophilic inflammation and patchy demyelination. Administration of corticosteroid with intravenous immunoglobulin and anakinra (IL-1 receptor antagonist) helped improve the white matter lesions and the clinical symptoms.

To date, only about 25 cases of genetically confirmed CFI deficiency have been reported. At the time of diagnosis, patient age ranged from infancy to 60 years, and clinical symptoms varied widely from severe bacterial infections to recurrent sterile neuroinflammations [36–38].

Phosphatidylinositol glycan anchor biosynthesis class T mutation

Advances in biochemical and genetic analysis are constantly revealing novel causes of recurrent aseptic meningitis. Recently, recurrent aseptic meningitis associated with phosphatidylinositol glycan anchor biosynthesis class T (PIGT) mutation has been reported [39]. A 71-year-old male experienced 121 episodes of recurrent aseptic meningitis over 18 years. Symptoms of meningitis improved spontaneously 7–10 days after onset. Corticosteroid treatment shortened the duration but was not effective in preventing the attacks. Prior to the occurrence of meningitis, he had a history of recurrent urticaria and arthralgia since the age of 30 years. At 68 years, the patient developed severe hemolysis and was diagnosed with paroxysmal nocturnal hemoglobinuria. Genetic analysis revealed no mutations in *MEFV*, *MVK*, *TNFRSF1A*, *NLRP3*, *NLRP12*, or *PIGA* but a germline nonsense mutation (c.250G>T, p.E84X) and a somatic 18 Mbp deletion in the *PIGT* gene. After administration of eculizumab, an anti-C5 antibody, all symptoms resolved, and the remission has lasted more than 3 years.

Neuronal intranuclear inclusion disease

Neuronal intranuclear inclusion disease (NIID) is a rare neurodegenerative disease characterized by eosinophilic hyaline intranuclear inclusions in the central, peripheral, and autonomic nervous systems. Since the first case reported in 1968, NIID has been considered a heterogeneous disease due to its highly variable clinical manifestations. Until 2011, about 40 NIID cases, which were diagnosed by postmortem brain biopsy, had been described worldwide. In recent years, skin biopsy and characteristic findings on brain MRI have been used to confirm NIID diagnosis; thus, the number of reported NIID cases has increased. Skin biopsy can detect intranuclear inclusions that are identical, both morphologically and immunohistochemically, to those found in central nervous tissues [40]. In 2019, a GGC repeat expansion in the 5'-UTR of *NOTCH2NLC* was shown as the genetic cause of NIID [41–43].

The onset age of NIID varies widely from infant to adult. The clinical manifestation of adult-onset NIID can vary, including

dementia, peripheral neuropathy, autonomic dysfunction, cerebellar ataxia, parkinsonism, seizure, and encephalitis episodes. Dementia is the most prominent symptom in sporadic cases of NIID. The majority of NIID cases have been reported from Japan, with an older age of onset (median, 60 years; interquartile range, 46–66 years) and large proportions of primary cognitive presentation (61%) and pathognomonic MRI changes (70%) [44]. Nervous system symptoms are the main manifestations of NIID; however, more than 10% of patients can present without nervous system symptoms. In a recent study, NIID was shown to present with diverse symptoms of other systems, especially respiratory, digestive, circulatory, and urinary systems [45]. Furthermore, the onset age of initial symptoms in different systems was much younger than that of disease in the nervous system [45].

The typical brain MRI findings are symmetrical leukoencephalopathy accompanied by high signal intensities along the corticomedullary junctions on diffusion-weighted imaging (DWI), termed the “zigzag edging sign.” [46]. However, only about 37% of affected individuals display typical MRI features [47]. Notably, these typical MRI features on DWI are also occasionally observed in fragile X tremor/ataxia syndrome (FX-TAS) caused by mildly expanded CGG repeats in the 5'-UTR of the *FMR1* gene and can show similar clinical presentation to NIID. Similar noncoding CGG repeat expansions (in LOC642361/NUTM2B-AS1) were identified in a newly described condition, oculopharyngeal myopathy with leukoencephalopathy, which also can show the typical MRI features [43]. Therefore, diagnostic utility of the zigzag edging sign in various clinical presentations should be further investigated.

The genetic diagnosis of NIID can be challenging, but noncoding CGG repeat expansion can be detected using various techniques. Repeat-primed polymerase chain reaction (PCR), GC-rich PCR, long-read sequencing using nanopore sequencing or single-molecule real-time sequencing, and whole genome sequencing can be utilized for diagnosis of NIID. To date, all confirmed cases of noncoding CGG repeat expansion have been reported in East Asian cohorts. The number of expanded CGG repeats ranged from 66 to 517 in NIID [41] and from 4 to 41 in healthy controls [47]. However, 7.1% of pathologically confirmed Japanese NIID patients did not contain CGG repeat expansion in NOTCH2NLC [43]. It is not clear whether anticipation occurs in NIID, like in other trinucleotide repeat disorders [45]. However, anticipation was recently observed in familial essential tremor patients with genetically confirmed NIID [47]. Therefore, there is need for further in-

vestigations in larger numbers of patients.

In a recent study, none of the 11 pathology-confirmed NIID cases of European ancestry carried the noncoding CGG repeat expansion, indicating that genetically heterogeneous mechanisms underlie NIID in European patients [44]. Therefore, CGG repeat expansions located in other loci or repeat expansions involving similar repeat motifs should be investigated in future studies. Conversely, the GGC repeat expansion in NOTCH2NLC has been identified in a small portion of Alzheimer disease-affected families (1.43%) and parkinsonism-affected families (1.46%) [41]. Therefore, NIID should be considered a differential diagnosis for dementia or parkinsonism. Some researchers suggest a concept of NIID-related disorder, which includes NIID and other related neurodegenerative disorders. NIIDs are likely underdiagnosed, and an efficient screening strategy should be established.

Currently, effective treatment to cure or slow the progression of NIID does not exist. Several medications can help improve patient symptoms, but research has been limited due to the small number of confirmed cases. Levodopa responsiveness in cases with parkinsonism is variable and unsustainable [48]. In a case report, two NIID patients presented with dopa-responsive juvenile parkinsonism. Both patients showed excellent initial response to levodopa treatment but soon experienced disabling dopa-induced dyskinesia [49]. In another case report, levodopa and trihexyphenidyl were ineffective against tremor in an NIID patient with resting tremor similar to that observed in Parkinson disease [50]. Therefore, levodopa responsiveness in NIID needs to be further investigated. Because NIID can currently be diagnosed using genetic testing, the number of reported NIID cases is rapidly increasing. The effectiveness of various treatments for NIID should be investigated in the near future.

Conclusion

Diagnosis of AE is increasing, and immunotherapies are delivered to many patients suspected of antibody-negative AEs. In addition, during the last decade, an increasing number of new diseases have been discovered due to diagnostic exome sequencing performed in many rare disease conditions. Differential diagnosis of rare genetic diseases in meningoencephalitis patients is important because it helps exclude the possibility of infection, and certain medications are effective in some cases. Further research on these rare diseases will significantly help these patients.

Conflicts of Interest

Jangsup Moon has been an associate editor of encephalitis since October 2020. He was not involved in the review process of this original article. No other potential conflict of interest relevant to this article was reported.

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