

Chorea in a patient with cryopyrin-associated periodic syndrome



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ABSTRACT

Objective: To describe a patient with cryopyrin-associated periodic syndrome (CAPS) with an uncommon neurologic phenotype and a rare underlying genetic mutation.

Results: Our patient had CAPS with a rare NLPR3 missense mutation (p.Tyr859Cys) in exon 6 with chorea as the major symptom. Clinical symptoms were associated with persistent inflammatory changes of the CSF and serum and included elevated anticardiolipin immunoglobulin G; MRI showed prolonged gadolinium enhancement of 2 chronic inflammatory lesions. Conventional immunosuppressive treatment with prednisolone and hydroxychloroquine was insufficient. Neurologic symptoms, laboratory/chemical measures, and MRI abnormalities almost completely normalized following interleukin (IL)-1 β blockade with anakinra.

Conclusions: This case is unique for its uncommon neurologic phenotype, the rare underlying genetic mutation, and the long course of the disease as well as almost complete recovery following appropriate therapy. In addition, the chronic inflammatory white matter lesions observed on brain MRI and the responsiveness to IL-1 β blockade with anakinra are unusual. *Neurology*® 2016;86:1-4

GLOSSARY

BBB = blood-brain barrier; **CRP** = C-reactive protein; **CAPS** = cryopyrin-associated periodic syndrome; **CINCA** = chronic infantile neurologic, cutaneous, arthritis; **EBV** = Epstein-Barr virus; **HHV** = human herpesvirus; **HSV** = herpes simplex virus; **IL** = interleukin; **MWS** = Muckle-Wells syndrome; **NOMID** = neonatal-onset multisystem inflammatory disease; **SAA** = serum amyloid A; **VZV** = varicella-zoster virus.

Cryopyrin-associated periodic syndrome (CAPS) is a rare but treatable monogenetic autoinflammatory condition due to a genetically determined overproduction of interleukin (IL)-1 β .¹ CAPS encompasses a clinical spectrum, ranging from milder manifestations of familial cold autoinflammatory syndromes and Muckle-Wells syndrome (MWS) to the most severe form of neonatal-onset multisystem inflammatory disease (NOMID), commonly referred to as chronic infantile neurologic, cutaneous, arthritis (CINCA) syndrome in Europe.^{2,3} Although amyloidosis with consequent renal failure determines life expectancy, neurologic complications are common in the NOMID phenotype.¹

We describe a patient with CAPS who also had antiphospholipid antibody syndrome, choreatic movements, and chronic inflammatory brain lesions on MRI. This patient responded well to IL-1 β blockade treatment.

This article provides Class IV evidence. It is a single case report without controls.

Case report. A 38-year-old woman first presented to our clinic in 2008 with a history of a steady progression of involuntary choreiform movements of the hands and feet. About 14 years prior, she first noticed some of these movements, but did not pay much attention to them. As the symptoms worsened, she could not suppress the movements, and eventually she felt increasingly constrained in her activities of daily living. Her medical history included inherited progressive hearing loss and rash since early childhood as well as myocarditis of unknown origin in 2001. At the time of examination, the patient further described episodes of fever and flush accompanied by arthralgia and lymph node swelling. Family history was positive for inherited deafness (mother, maternal uncle, brother; figure 1). The patient's mother had died of chronic kidney failure caused

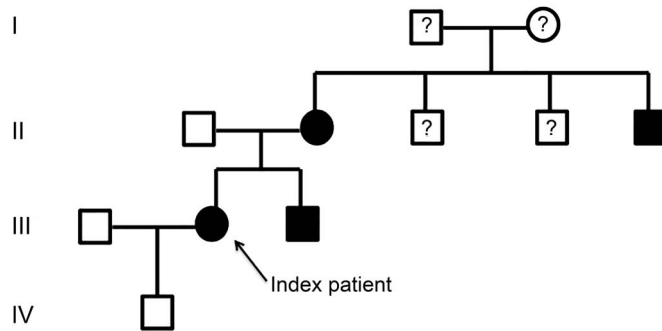
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Figure 1 Family tree of the index patient (III-2)



Solid symbols represent family members with inherited deafness and suspected cryopyrinopathy. Open symbols indicate healthy relatives. Question mark indicates insufficient data available from patient. The patient's mother (II-2) also had fibrinogen A α -chain amyloidosis and died of chronic kidney failure.

by serum amyloid A (SAA) amyloidosis (histologically confirmed by renal biopsy). Physicians suspected MWS, but the patient's mother refused genetic testing. In 2005, the patient gave birth to a premature boy; her son's development continues unremarkably to date (including genetic testing).

The patient was a slender Caucasian woman with bilateral deafness. Neurologic examination revealed intermittent darting movements of the tongue and pronounced bilateral choreatic movements of the hands and feet with irregular nonrhythmic movements of the fingers. These movements could not be suppressed and were increased by activity or emotional stress (video 1 on the *Neurology*[®] Web site at Neurology.org). Neuropsychological examination showed mild deficits in attention and executive function including reduced lexical fluency and reduced visual-spatial short-term memory.

The patient had an increased leukocyte count and C-reactive protein (CRP) (laboratory results are summarized in the table). Urinalysis showed mild proteinuria. CSF examination revealed mild pleocytosis (33 cells/ μ L; 65% neutrophils, granulocytes, 15% lymphocytes, and 20% monocytes) with elevated total protein and positive oligoclonal bands. Serologic examinations in blood and CSF (HIV, herpes simplex virus [HSV] 1/2, varicella-zoster virus [VZV], Epstein-Barr virus [EBV], human herpesvirus [HHV]-6, adenovirus, tick-borne encephalitis virus, *Borrelia*, *Treponema pallidum*) as well as screening for neurotropic viruses in CSF using multiplex PCR (for HSV 1/2, VZV, EBV, HHV-6) were all normal or negative. Immunologic workup revealed only a markedly elevated anticardiolipin immunoglobulin G and slightly elevated antinuclear antibody level (1/160); screening for anti- β 2-glycoprotein, rheumatoid factor, anti-double-stranded DNA antibodies, and complement factors (C3, C4) was normal. Serum amyloid A level was elevated. Genetic testing for Huntington disease (OMIM 143100) and Huntington disease-like 1 (OMIM 603218) and 2 (OMIM 606438) was negative. Brain MRI initially showed extensive white matter changes localized bilaterally predominantly in the periventricular and subcortical white matter with gadolinium enhancement in 2 of these lesions (figure 2). 3D time-of-flight magnetic resonance angiography as well as funduscopy and transcranial color-coded duplex sonography did not reveal aspects of cerebral vasculitis.

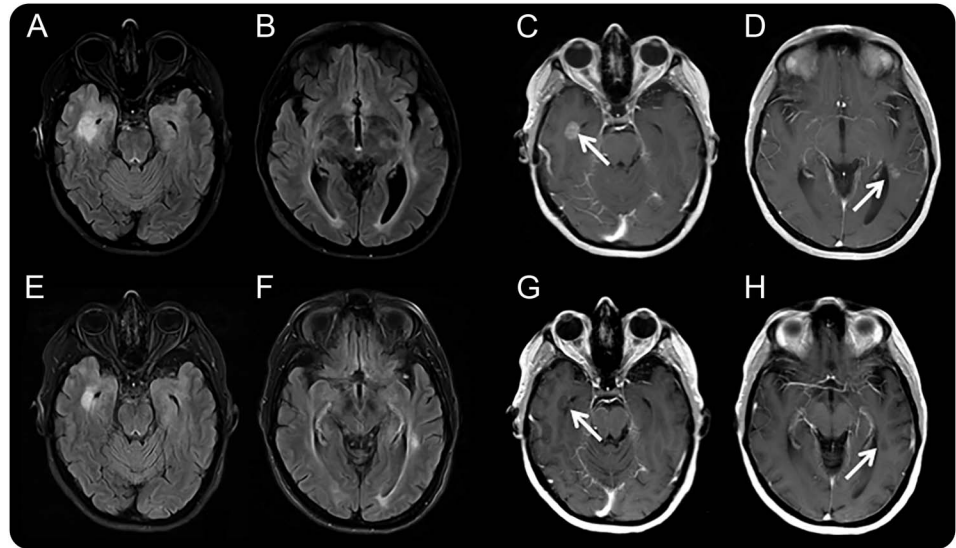
Clinical course. We started immunosuppressive treatment with 50 mg prednisolone and 200 mg hydroxychloroquine because of suspected primary antiphospholipid antibody syndrome.^{4,5} Following 4 months of treatment, choreiform symptoms improved, but did not fully subside. Serum anticardiolipin antibody levels decreased, but

Table Laboratory results at initial presentation in 2008, under immunosuppressive treatment with prednisolone and hydroxychloroquine in 2010, 2011, and 2012 directly before initiation of interleukin-1 blockade treatment, and under treatment with anakinra in 2013 and 2014

	Standard value	Year of testing					
		2008	2010	2011	2012	2013	2014
Leukocyte count/ μ L	4,200-10,200	11,120	10,420	18,060	14,180	6,530	4,820
C-reactive protein, mg/L	0-5	64.6	36	58.7	38	<2.9	<2.9
Anticardiolipin IgG, U/mL	0-10	29.1	26.8	11.8	10.2	5.5	NT
Anticardiolipin screen, U/mL	0-10	17.9	18.2	16.1	11.6	10.7	7.7
Serum amyloid A, mg/dL	<0.5	NT	NT	NT	29.6	0.63	0.59
Proteinuria, mg protein/g urine creatinine	<100	163	NT	119	166	75	87
CSF							
Cell count/ μ L	0-5	33	32	68	15	1	NT
Protein, mg/L	200-400	790	645	642	679	455	NT
Oligoclonal bands	Negative	Positive	Positive	Positive	Positive	Positive	NT

Abbreviations: IgG = immunoglobulin G; NT = not tested.

Figure 2 MRI before (A-D) and after treatment (E-H) with anakinra



Fluid-attenuated inversion recovery images (A, B and E, F) show notable periventricular and subcortical chronic white matter lesions with partial gadolinium enhancement (arrows) on T1 images (C, D), which persisted with immunosuppression with prednisolone and hydroxychloroquine treatment, but subsided after treatment with anakinra (G, H).

we observed persistent mild pleocytosis in CSF (increased leukocytes, SAA, CRP) and proteinuria (table). In addition, we observed essentially unchanged gadolinium enhancement of inflammatory lesions on MRI (figure 2); however, there were no new gadolinium-enhancing lesions identified on follow-up imaging.

Independent of the neurologic clinical course, the development of proteinuria, taken together with the family history and persistent elevation of CRP and SAA levels, led us to consider genetic testing in this patient. Genetic testing results revealed a rare *NLPR3* missense mutation (p.Tyr859Cys) in exon 6 previously associated with the NOMID phenotype of the cryopyrin-associated periodic syndrome (CAPS).^{6,7} In addition to the existing immunosuppression, we initiated disease-specific IL-1 β blockade with anakinra (subcutaneous injection, 100 mg daily). With treatment, choreiform symptoms disappeared almost completely (video 2) even after discontinuing prednisolone and hydroxychloroquine therapy. Neuropsychological follow-up examination revealed substantial improvements in all areas tested. Consistent with the clinical course, the laboratory test results returned normal levels (table). Persistent gadolinium enhancement of MRI brain lesions, which previously were unaffected by immunosuppression with prednisolone and remained fairly unchanged over years, also disappeared following anakinra treatment.

DISCUSSION Previously described neurologic manifestations in patients with a more severe form of CAPS, the NOMID/CINCA phenotype, commonly include headache and migraine, sometimes accompanied by aseptic meningitis and increased intracranial

pressure, cognitive disability, sensorineural hearing loss (following inner ear inflammation), papilledema, and myalgia.¹ Our patient is unusual, with CAPS and severe chorea accompanied by chronic inflammatory lesions of the CNS as observed on MRI. Similar MRI and CSF abnormalities, accompanied by progressive hearing loss and rash, have also been reported in Susac syndrome, which is characterized by the triad of subacute encephalopathy, visual disturbances, and sensorineural hearing loss, but may also present with only of a subset of these symptoms.^{6,7} However, the long and continuous course of the disease with onset of sensorineural hearing loss in early childhood as well as proteinuria and especially inheritance do not support this differential diagnosis. The presence of CAPS and its etiology is finally confirmed by the clinical and serologic results of anti-IL-1 therapy and, above all, by diagnosis of a rare (TGT)-/p.Tyr859Cys-/Y859C-substitution in exon 6 of the *NLPR3* gene. We found this mutation to be reported twice before, once in a French family who shared a phenotype consisting of febrile episodes, bilateral sensory hearing loss, myalgia, arthralgia, uveitis/papillitis, headache, and aseptic meningitis, and once in a 16-year-old boy from the Netherlands with a de novo mutation and a “predominantly neurological phenotype,” which was not fully described in the brief report.^{8,9} Neither of these publications described neurologic manifestations with regard to the movement disorder. Although chorea has not been reported in patients with CAPS, choreatic movements are occasionally reported in patients with systemic lupus erythematosus and may be associated with antiphospholipid antibody syndrome.^{4,5} If

pathogenic antibodies cause chorea by binding to yet unknown antigens in the CNS, this requires disruption of the blood–brain barrier (BBB) to gain access to locally accumulated IL-6, interferon- α , and IL-1.¹⁰ Thus, the distinct clinical phenotype may be explained by the colocalization of antiphospholipid antibodies with CAPS-dependent asymptomatic meningitis and consecutive BBB damage (as observed on MRI and CSF examination) due to IL-1 β overexpression.

We described chronic inflammatory brain white matter lesions associated with antiphospholipid antibody syndrome in a patient with progressive choreatic movements and an NLRP3 missense mutation (p.Tyr859Cys) in exon 6. The case is unique not only because of the long course of the disease with almost complete recovery following appropriate therapy, but also because of the rare underlying genetic mutation, and the responsiveness of MRI lesions to IL-1 β blockade with anakinra.

AUTHOR CONTRIBUTIONS

Christopher J. Schwarzbach contributed to the manuscript, data acquisition, data interpretation, video acquisition, and video processing. Wilhelm H. Schmitt contributed to the manuscript, data acquisition, and interpretation. Kristina Szabo contributed to the manuscript, data acquisition, and data interpretation. Hansjörg Bänzner contributed to the manuscript and data and video acquisition. Michael G. Hennerici contributed to the manuscript, data acquisition, and interpretation. Christian Blahak contributed to the manuscript, data acquisition, data interpretation, video acquisition, and video processing.

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REFERENCES

1. Kitley JL, Lachmann HJ, Pinto A, Ginsberg L. Neurologic manifestations of the cryopyrin-associated periodic syndrome. *Neurology* 2010;74:1267–1270.
2. Hawkins PN, Lachmann HJ, Aganna E, McDermott MF. Spectrum of clinical features in Muckle-Wells syndrome and response to Anakinra. *Arthritis Rheum* 2004;50:607–612.
3. Glödbach-Mansky R. Current status of understanding the pathogenesis and management of patients with NOMID/CINCA. *Curr Rheumatol Rep* 2011;13:123–131.
4. Cervera R, Asherson RA, Font J, et al. Chorea in the antiphospholipid syndrome: clinical, radiologic, and immunologic characteristics of 50 patients from our clinics and the recent literature. *Medicine* 1997;76:203–212.
5. Orzechowski NM, Wolanskyj AP, Ahlskog E, Kumar N, Moder KG. Antiphospholipid antibody-associated chorea. *J Rheumatol* 2008;35:2165–2170.
6. van der Kooij SM, van Buchem MA, Overbeek OM, Dijkman G, Huizinga TW. Susac syndrome: a report of four cases and a review of the literature. *Neth J Med* 2015;73:10–16.
7. Greco A, De Virgilio A, Gallo A, et al. Susac's syndrome: pathogenesis, clinical variants and treatment approaches. *Autoimmun Rev* 2014;13:814–821.
8. Jeru I, Marlin S, Le Borgne G, et al. Functional consequences of a germline mutation in the leucine-rich repeat domain of NLRP3 identified in an atypical autoinflammatory disorder. *Arthritis Rheum* 2010;62:1176–1185.
9. Frenkel J, van Kempen MJ, Kuis W, van Amstel HK. Variant chronic infantile neurologic, cutaneous, articular syndrome due to a mutation within the leucine-rich repeat domain of CIAS1. *Arthritis Rheum* 2004;50:2719–2720.
10. Baizabal-Carvallo JF, Bonnet C, Jankovic J. Movement disorders in systemic lupus erythematosus and the antiphospholipid syndrome. *J Neural Transm* 2013;120:1579–1589.

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