

A case of neonatal onset multisystem inflammatory disease supporting a role of interleukin-1 β in moyamoya syndrome

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Moyamoya syndrome (MMS) is a chronic progressive cerebrovascular condition characterized by bilateral stenosis/occlusion of the terminal internal carotid artery (ICA) often extending to neighboring cerebral arteries with prominent collateral circulation and increased risk of hemorrhage. Symptoms include stroke, TIA, and headache.¹ MMS's etiology is unknown. However, experimental evidence from arterial smooth muscle cells (SMC) derived from patients with MMS has suggested that interleukin-1 beta (IL-1 β)-dependent prostaglandin overproduction plays a crucial role in its pathogenesis.² Neonatal onset multisystem inflammatory disease (NOMID) is an autosomal dominantly inherited disease characterized by excessive IL-1 β -overproduction and autoinflammation. Accordingly, NOMID is treated with IL-1 receptor antagonists such as anakinra (Kineret, Swedish Orphan Biovitrum AB, Sweden, Stockholm) or IL-1 receptor antibodies such as canakinumab (Ilaris, Novartis, Basel, Switzerland).³ We here report the development of MMS in a NOMID patient. In this patient, escalation of IL-1 receptor antagonistic treatment led to a significant reduction of disease activity and TIAs. Both the occurrence of MMS in this NOMID patient and the clinical and laboratory improvement because of IL-1 receptor antagonism provide direct clinical evidence that IL-1 β overproduction could play a pathophysiologic role in MMS.

Case report

A novel NOMID-causing mutation (S331R mutation of the CIAS1 gene) was identified and published when the patient was 4 years old.⁴ Genetic testing was performed because the patient showed neonatal onset urticaria-like rash, fever, laboratory findings of systemic inflammation, hepatosplenomegaly, facial features with frontal bossing and saddleback nose, arthritis, and chronic inflammation of the CNS with sensorineural deafness. The mutation led to an overproduction of IL-1 β , multisystem autoinflammation, and aseptic meningitis characterized by blood-brain barrier impairment (BBBI). His symptoms showed an excellent response to IL-1 receptor antagonistic treatment with anakinra.⁴ NOMID disease activity remained well controlled until the age of 16 when anakinra was discontinued and treatment with canakinumab was started. Anakinra requires a daily subcutaneous application, whereas canakinumab is more practical because it is only administered once in every 8 weeks. However, at age 19, the patient presented to our stroke unit with a 2-year history of occipital headache and recurrent, increasingly more intense and frequent TIAs associated with hypesthesia of the right upper limb. Digital subtraction angiography showed occlusion of the left terminal ICA/anterior cerebral artery (A1)/middle cerebral artery (M1) segment with MMS-typical prominent arterial collateral circulation and stenosis of the right ICA/A1/M1 segment (figure e-1, links.lww.com/NXI/A339). CSF analysis demonstrated pleocytosis (368/ μ L) and elevated protein (889.5 mg/L) indicating BBBI. CSF cytokines IL-1 β , IL-6, and interferon-gamma induced protein 10

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Table CSF and serum analysis before treatment with IL-1 antagonists at the age of 4 years⁴ (before IL-1 antagonists), under canakinumab treatment at admission to our unit at the age of 19 years (canakinumab), 1 week after treatment escalation from canakinumab to high-dose anakinra (1-week anakinra) and 3 months later under continued treatment with high-dose anakinra (3 months anakinra)

	Before IL-1 antagonists ⁴	Canakinumab	1-week Anakinra	3-months Anakinra
Serum				
C-reactive protein (mg/L)	93	23	4.8	2.5
Leukocytes (/nL)	18.2	10.2	5.3	5.4
Serum-amyloid A (mg/mL)	250	317	3	-
IL-1 β (pg/mL)	-	21	172	76
IL-6 (pg/mL)	-	4.0	<2.0	<2.0
IP-10 (pg/mL)	-	598	198	-
Calprotectin (μ g/mL)	-	7.8	2.2	2.6
CSF				
IL-1 β (normal range: 0.36–0.74 pg/mL)	-	14.3	5.8	-
IL-6 (normal range: 2.0–5.8 pg/mL)	-	923	4.8	-
IP-10 (normal range: 211–423 pg/mL)	-	2,446	623	-
Cell count (/ μ L)	Elevated	368	47	29
Protein (mg/L)	Elevated	889.5	411.5	395.1

Pathologic changes are marked in bold. “-” indicates when values were not measured.

kD (IP-10) were significantly increased (table). No infectious agents were detected. Serum analysis revealed elevated inflammatory markers and cytokines including IL-1 β , IL-6, and IP-10 (table). We changed treatment from canakinumab to high-dose anakinra 8 mg/kg body weight/d based on a previous study of CSF biomarkers that had suggested superiority of anakinra over canakinumab especially in the intrathecal compartment.⁵ Follow-up CSF analysis showed a significant decrease of pleocytosis (47/ μ L), normal protein levels (412 mg/L), and a significant reduction of CSF cytokines after only 1 week. Simultaneous serum analysis showed reduced inflammatory parameters (table). At the follow-up 3 months later, the patient showed a near-complete clinical recovery with no further TIAs and significantly less headache. CSF analysis revealed even milder pleocytosis (29/ μ L) and normal protein content (395 mg/L). Serum analysis demonstrated no signs of systemic inflammation anymore (table). MRI and magnetic resonance angiography vessel wall imaging did not reveal changes.

Discussion

The etiology of MMS is largely unknown. However, BBBI is characteristic for MMS and has been suggested to play a role in MMS pathogenesis.^{6,7} Experimental findings in arterial SMCs of patients with MMS without NOMID additionally indicated an important role of IL-1 β -induced prostaglandin E₂ (PGE₂) overproduction, decreasing vascular tone, increasing vascular

permeability, promoting intimal thickening, and mediating inhibitory effects on growth and migration of SMCs.² It is interesting in this respect that NOMID involves IL-1 β associated BBBI and that our patient with NOMID- and IL-1 β -associated aseptic meningitis and BBBI developed MMS.⁵ The causal importance of IL-1 β was further supported by our findings that the systemic inflammation, the inflammatory CSF markers, the elevated CSF protein indicating BBBI, and the recurrent TIAs responded well to the treatment escalation from canakinumab to high-dose anakinra. If the previous experimental hypothesis is correct that IL-1 β -induced PGE₂ overproduction is an important pathway in MMS pathogenesis, NOMID should be a strong risk factor for MMS. This is suggested by the present report and should be further studied in a larger cohort. On the other hand, IL-1 β antagonistic treatment could be an interesting option for the treatment of MMS in patients without NOMID, if the IL-1 β pathway is generally involved in the pathogenesis of MMS. For example, MMS can be associated with trisomy 21, hyperthyroidism, sickle cell disease, and cranial irradiation in all of which IL-1 has been implicated. Thus, it is speculative at this point in time and should nevertheless be mentioned that NOMID could be a Mendelian model disease for MMS. This places our case in the emerging literature on genetic, autoinflammation-related vasculopathies that also include other MMS-associated conditions, such as, for example, mutations in the SAMHD1 gene.

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Disclosure

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Name	Location	Contribution
Felix Wohlrab, MD	Charité–Universitätsmedizin Berlin	Designed the study and participated in drafting and reviewing
Christian Bauknecht, MD	Charité–Universitätsmedizin Berlin	Performed the neuroradiologic assessment and participated in drafting and reviewing

Appendix (continued)

Name	Location	Contribution
Christian Meisel, MD	Charité–Universitätsmedizin Berlin	Supervised and assessed the laboratory tests and participated in drafting and reviewing
Jens P. Dreier, MD	Charité–Universitätsmedizin Berlin	Designed the study and participated in drafting and reviewing

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