Expanding the RNF213 Phenotype: Very Early-Onset, Rapidly Progressive Moyamoya Disease with Poor Collateral Vessel Development in an Infant

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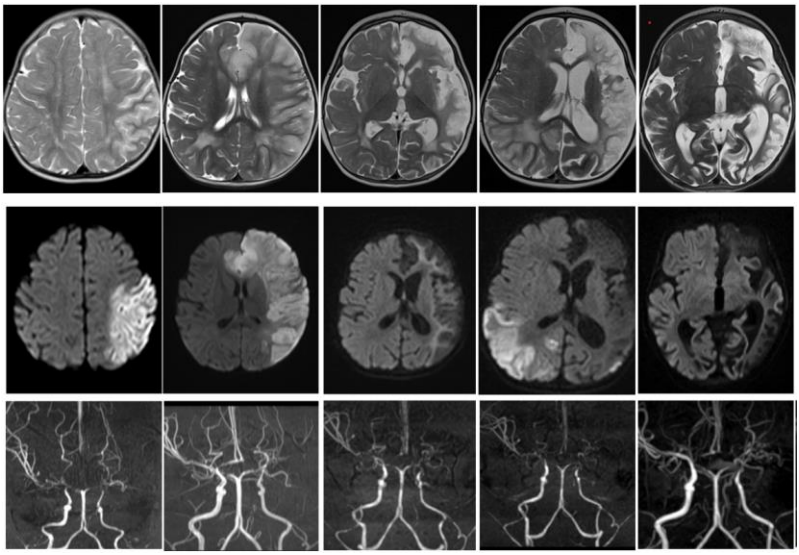
Objectives: Moyamoya angiopathy (MMA) is a rare, progressive cerebrovascular disorder characterized by stenosis or occlusion of the internal carotid arteries (ICAs) and their main intracranial branches, resulting in the development of fragile collateral networks known as «Moyamoya vessels». These aberrant vessels may involve both anterior and posterior circulations, predisposing to multiple focal cerebral injuries. In pediatric patients, arterial ischemic strokes (AIS) and transient ischemic attacks (TIAs) are the predominant clinical manifestations, while hemorrhagic strokes are more frequent in adults.

Methods: A previously healthy 13-month-old female presented with acute right hemiparesis 10 days following MMR and varicella vaccinations. Initial neuroimaging revealed an AIS in the left middle cerebral artery (MCA) territory. Based on clinical context and imaging, inflammatory focal cerebral arteriopathy (FCA-i) was initially suspected. Cerebrospinal fluid (CSF) analysis was normal, with no evidence of infection. Nevertheless, empirical treatment with antibiotics, antivirals, acetylsalicylic acid, and subsequently high-dose methylprednisolone was initiated. A follow-up MRI demonstrated infarct progression involving both MCA and anterior cerebral artery (ACA) territories. The patient was transferred to a tertiary pediatric neurology unit, where she experienced focal seizures and persistent left hemiparesis. EEG identified right frontal epileptiform activity, and lacosamide therapy was started. Intravenous immunoglobulin was administered without clinical improvement. Extensive diagnostic work-up ruled out cardiac, hematologic, metabolic, and autoimmune etiologies. Whole genome sequencing identified a heterozygous de novo c.11999G>T (p.Cys4000Phe) missense variant in the RNF213 gene. This variant, not previously reported in population databases or scientific literature, was classified as likely pathogenic (ACMG Class 4). The diagnosis of Moyamoya disease (MMD) was confirmed based on bilateral ischemic lesions and the presence of collateral vessel formation. Three months later, the patient developed additional focal motor seizures and new ischemic events. After two months of clinical stabilization, indirect revascularization surgery was performed.



Conclusion: RNF213 encodes a protein implicated in vascular homeostasis and is the principal genetic susceptibility factor for MMD. Although the precise function of RNF213 remains unclear, pathogenic Variantsâ ”particularly de novo mutationsâ€”are associated with an aggressive disease course. This case highlights a rapidly progressing MMD phenotype with early bilateral vessel involvement and recurrent ischemia. Prompt recognition of such phenotypes is essential for early diagnosis and management. Genetic and radiological evaluations are crucial in guiding therapeutic decisions and improving prognosis in pediatric MMD patients.

24-28 Ottobre 2025
Padova Congress
55° CONGRESSO SOCIETÀ ITALIANA DI NEUROLOGIA