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CASE REPORT

Neurodegeneration, Intracranial Calcifications, Microcephaly and Drug-Resistant Epilepsy Caused by a Novel Homozygous Missense Variant in the *NRROS* Gene: A Case Report

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Abstract: Negative regulator of reactive oxygen species (*NRROS*)-related microgliopathy (MIM# 618875) is a rare autosomal recessive neurodegenerative disorder. This case report describes a Saudi Arabian child with a novel homozygous *NRROS* variant, NM_198565.2: c.257T>C (p.Leu86Pro) presenting with drug-resistant epilepsy, rapid developmental regression, microcephaly, dystonia, and intracranial calcifications. Neuroimaging revealed bilateral intracranial calcifications, generalized brain volume loss, and connatal cysts; EEG showed a slow, suppressed background with multifocal epileptiform discharges. The variant is predicted to be deleterious by multiple in silico tools, suggesting a pathogenic effect on microglial function. This case underscores the importance of considering *NRROS*-related microgliopathy in children with early-onset neurodegeneration, drug-resistant epilepsy, and intracranial calcifications, enabling targeted genetic testing, diagnosis, and counseling.

Keywords: *NRROS* gene, microgliopathy, intracranial calcification

Introduction

Negative regulator of reactive oxygen species (*NRROS*)-related microgliopathy, a rare and recently recognised neurodegenerative disorder, is caused by pathogenic variants of the *NRROS* gene.[1] *NRROS* encodes a leucine-rich repeat transmembrane protein expressed predominantly in microglia within the CNS.[1,2] It regulates reactive oxygen species (ROS) by modulating NADPH oxidase 2 (NOX2) stability,[2] influences Toll-like receptor signaling,[3] and activates latent transforming growth factor-β1 (TGF-β) complexes.[4] Disruption of NRROS impairs microglial development and function, contributing to neurodegeneration.[1] In 2020, Dong et al reported six patients from four families with biallelic variants of *NRROS* gene.[5] All patients had neurodegenerative disorders with drug-resistant epilepsy (DRE), developmental regression, and reduced white matter volume.[5] In 2022, Madaan et al reported a novel, homozygous likely pathogenic *NRROS* variant in a child presenting with infantile epileptic spasms syndrome followed by progressive neurodegeneration.[6] Macintosh et al reported a novel biallelic variant of *NRROS* associated with neurodegeneration, intracranial calcification, and lethal microgliopathy.[7] To date, 12 patients have been reported to have pathogenic variants in *NRROS*,[7,8] and this report provides insight into this condition in a Saudi child with a novel *NRROS* variant to improve the understanding of this rare disease and its phenotypic spectrum.

Case Report

A 23-months-old Saudi girl presented with epilepsy and developmental regression at the age of 16 months. She was born to a consanguineous Saudi parents, following an uneventful pregnancy and delivery, and had normal development until

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12-months of age, when she started to lose acquired skills and had focal, motor-unaware seizures. She was diagnosed with focal epilepsy that was initially well-controlled with levetiracetam. She continued to regress in all milestone domains and her epilepsy evolved into DRE. The typical semiology of her seizures included: 1) focal, unaware, motor seizures with behavioural arrest, blank stare, nystagmoid eye movements, and left-sided clonic facial and arm movements. 2) generalized tonic-clonic seizures. 3) generalized myoclonic seizures. Seizures failed to be controlled with valproic acid, clobazam and topiramate and the patient was started on a ketogenic diet. She showed partial seizure control on the ketogenic diet; however, it was discontinued due to suboptimal response and resistant metabolic acidosis. At 24 months of age, the patient developed generalised dystonia and presented with status dystonicus in the context of pneumonia. Physical examination at that time revealed microcephaly, head circumference 43.5 cm (below 3rd percentile for age), axial hypotonia, and appendicular hypertonia; otherwise, neurological and systemic examination was unremarkable. At the age of 30 months, she was re-admitted with pneumonia requiring prolonged mechanical ventilation. Despite extubation, she remained dependent on non-invasive respiratory support. At her last follow-up, the neurological examination remained unchanged, with microcephaly, axial hypotonia, and appendicular hypertonia. Computed tomography (CT) of the brain showed bilateral subcortical and periventricular hyperdense foci, indicative of calcification (Figure 1). Brain magnetic resonance imaging (MRI) showed generalised brain volume loss with multiple foci of hyperintensities in susceptibility-weighted imaging (SWI) sequences, suggestive of intracranial calcifications and bilateral connatal cysts (Figure 2). EEG revealed a slow, suppressed background with multifocal interictal epileptiform discharges over the central head regions. Chromosomal microarray analysis did not reveal any genetic alteration. Whole exome sequencing revealed a homozygous missense *NRROS* variant NM_198565.2: c.257T>C (p.Leu86Pro). Carrier testing confirmed a heterozygous state in both the parents and siblings. The variant identified in the reported child was not found in the gnomAD genomes, v4.1.0. In silico predictions of this variant were assessed using EIGEN, EVE,

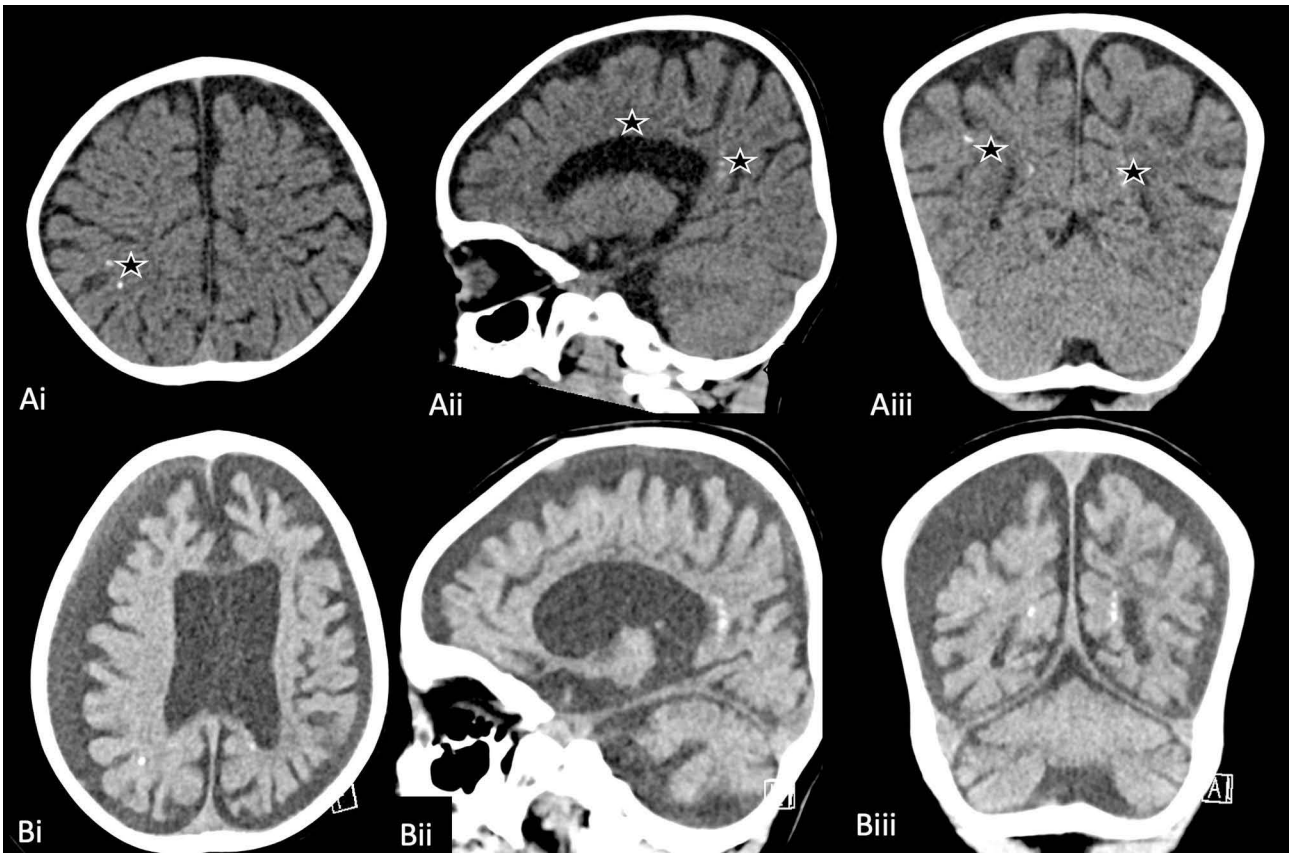

Figure 1 Axial non-contrast head CT at presentation (**Ai–Aiii**) demonstrates punctate calcifications in the subcortical and periventricular regions (black star). A follow-up imaging after 12 months (**Bi–Biii**) reveals progressive cerebral volume loss and ventriculomegaly.

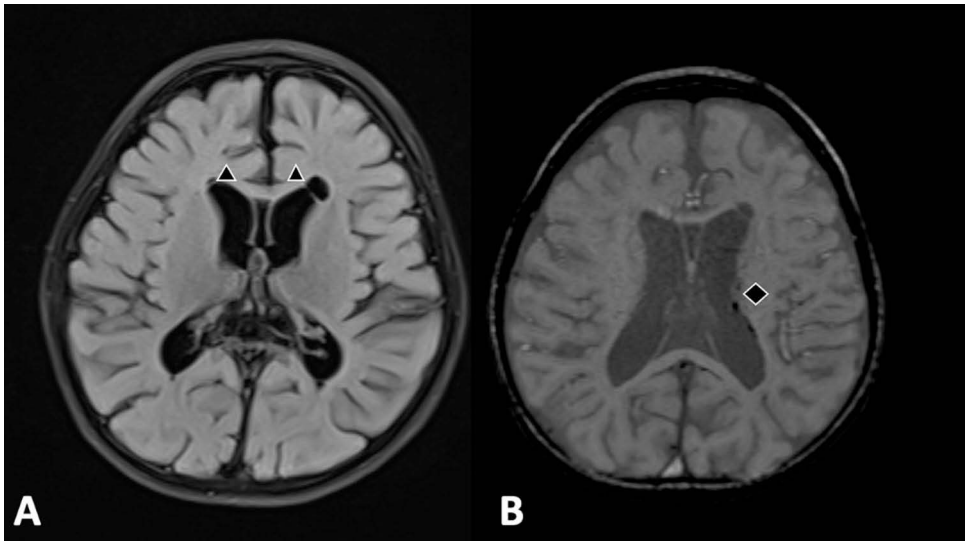

Figure 2 Brain MRI demonstrates generalized cerebral volume loss with bilateral connatal cysts (black triangle) on FLAIR sequence (**A**), and foci of intracranial calcifications (black diamond) on SWI sequence (**B**).

FATHMM-XF, MutPred, and PROVEAN and a high probability of the variant being pathogenic was observed. Pathogenic variants of *NRROS* are known to cause autosomal recessive encephalopathy with neurodegeneration, intracranial calcification, cerebral atrophy, and drug-resistant epilepsy.

Discussion

NRROS-related microgliopathy is an autosomal recessive condition caused by homozygous or compound heterozygous pathogenic variants of the *NRROS* gene.[1] *NRROS* is required for the expression of microglial genes that are essential for microglial development and function.[9] A previous report of six children with early onset seizures, neurodegeneration, and brain calcifications (SENEBAC) due to bi-allelic germline variants in the *NRROS* gene.[5] Similar to our patient, all affected children were hypotonic, with variable seizure types that evolved to refractory epilepsy and rapid progressive developmental regression after seizures onset.[5] Three affected children from two unrelated families developed drug-resistant epilepsy following a period of normal development.[5] Like our patient, the affected children continued to regress in motor skills.[1,5] Published cases show a uniformly severe course, with onset of neurodegeneration and DRE in the second year of life, leading to death by 3 years of age, and the eldest surviving child is nine years old.[1,5] Of note, our patient presented with dystonia, which has been previously reported only in one patient.[6] Brain imaging showed marked progressive brain volume loss, signal changes in the cerebral and cerebellar white matter, punctate calcifications, and about half the patients also had hypoplasia of the corpus callosum.[1,5] Previously described *NRROS* gene variants include homozygous *NRROS* variants: c.1777C > T (p.Gln593*) and a c.1257del (p.Gly420Alafs*14),[1] a homozygous frameshift variant c.1981delC (p.Leu661Serfs*97) reported in three patients,[5] a homozygous, frameshift variant c.1359del (p.Ser454Alafs*11),[6] and a missense variant c.185T>C (p.Leu62Pro), a premature stop codon c.310C>T (p.Gln104*).[7] In addition, a homozygous frameshift variant c.1644delG (p.Thr549Profs*82) was reported in one patient,[5] and another patient was found to have compound heterozygosity for two NRROS variants: a missense variant c.29T>C (p.Leu10Pro) and a frameshift variant c.190delC (p.Leu64Trpfs*81).[5] A recently reported child with a novel *NRROS* loss-of-function variant c.720G>A (p.Trp240*) presented with developmental regression, refractory seizures, and intracranial calcifications, along with dysmorphism and areflexia, features that broaden the known phenotypic spectrum.[10] This is the first report of a child from Saudi Arabia with a novel variant of the *NRROS* gene c.257T>C (p.Leu86Pro) with phenotypic and radiological features consistent with those of previously described cases. The clinical presentation of developmental regression, DRE, intracranial calcifications, and microcephaly is not specific to *NORRS*-related microgliopathy and may overlap with other genetic neurodegenerative disorders such as Aicardi-Goutières

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syndrome, mitochondrial encephalopathies or congenital cytomegalovirus (CMV) infections. A comprehensive diagnostic approach is therefore essential to determine the underlying etiology.

Neuropathological findings in a previously reported patient demonstrated central nervous system (CNS)-restricted pathology with marked cerebral atrophy, diffuse grey and white matter involvement, neuronal loss, gliosis, and perivascular accumulation of foamy macrophages.[1] These cells were positive for CD68 and MHC Class II markers but lacked expression of homeostatic microglial markers such as P2Y12, TMEM119, and IBA1.[1] White matter also showed reduced myelin basic protein (MBP), indicating demyelination.[1] NRROS deficiency leads to abnormal microglial morphology and loss of homeostatic markers, as seen in both patient tissues and *Nrros*-knockout mouse models.[1] Pathological examination of another affected child revealed both extensive grey and white matter involvement, dystrophic calcifications, and infiltration of foamy macrophages with a mitochondrial ultrastructure abnormality noted on electron microscopy.[7] This microglial dysfunction may underlie the progressive neurodegeneration seen in affected individuals.

Conclusion

This report describes a novel *NRROS* variant associated with a phenotype consistent with previously reported cases, contributing to the expanding clinical and radiological spectrum of *NRROS*-related microgliopathy. Early recognition of this disorder is essential for accurate diagnosis and genetic counseling, particularly given its autosomal recessive inheritance and a 25% recurrence risk in future pregnancies. It also underscores the need for further research to elucidate the full phenotypic spectrum and underlying pathophysiological mechanisms of *NRROS*-related disorders, which could inform future diagnostic, prognostic, and therapeutic approaches in pediatric neurology and clinical genetics.

Ethics Approval and Informed Consent

The case report was prepared after obtaining informed consent from the patient's parents. Written informed consent for publication of their details was obtained from the parents. The patient's parents understand that the patient's name and initials will not be published, and efforts will be made to conceal his identity; however, anonymity cannot be guaranteed. IRB approval was obtained from the Imam Abdulrahman Bin Faisal University (IRB# 2024-01-526).

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Disclosure

The author reports no conflicts of interest in this work.

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