Autosomal recessive *NOTCH3*-related leukodystrophy in two siblings

Fatema Al Amrani (1), Almundher Al-Maawali (2), Khalid Al-Thihli (2), Eiman Al Ajmi (3), Anuradha Ganesh (4), Amna Al Futaisi (5)

(1) Peditaric Neurology Unit, Department of Child Health, Sultan Qaboos University Hospital (2) Department of Genetics , Sultan Qaboos University Hospital (3) Department of Radiology and Molecular Imaging, Sultan Qaboos University Hospital (4) Department of Ophthalmology, Sultan Qaboos University Hospital (5) Department of Child Health, College of Medicine, Sultan Qaboos University Hospital, Sultan Qaboos University, Muscat, Oman

ICNC 2022
17th INTERNATIONAL CHILD NEUROLOGY CONGRESS
ANTALYA, TURKEY | OCTOBER 3-7, 2022

Background

- ***NOTCH3*** is a large type I transmembrane receptor that is primarily expressed on small artery smooth muscle cells and pericytes surrounding capillaries.
- **Cerebral autosomal dominant (AD) arteriopathy with subcortical infarcts and leukoencephalopathy** (CADASIL, OMIM:125310) is caused by **missense** mutations in the *NOTCH3* gene, causing a severe cerebral vasculopathy that targets microcirculation and perfusion.
- A novel phenotype caused by **biallelic null mutations** in *NOTCH3* has been reported (1-3).

Objectives

- To describe two cases with homozygous loss of function variants in *NOTCH3* along with the clinical manifestations and neuroimaging findings.

Clinical Report

- Two siblings presented with clinical manifestations including eye misalignment, visual impairment, epilepsy, global developmental delay and subsequent development of pyramidal signs in the first year of life.
- Livido reticularis was not reported in our cases despite the fact that it was present in most previously reported patients.

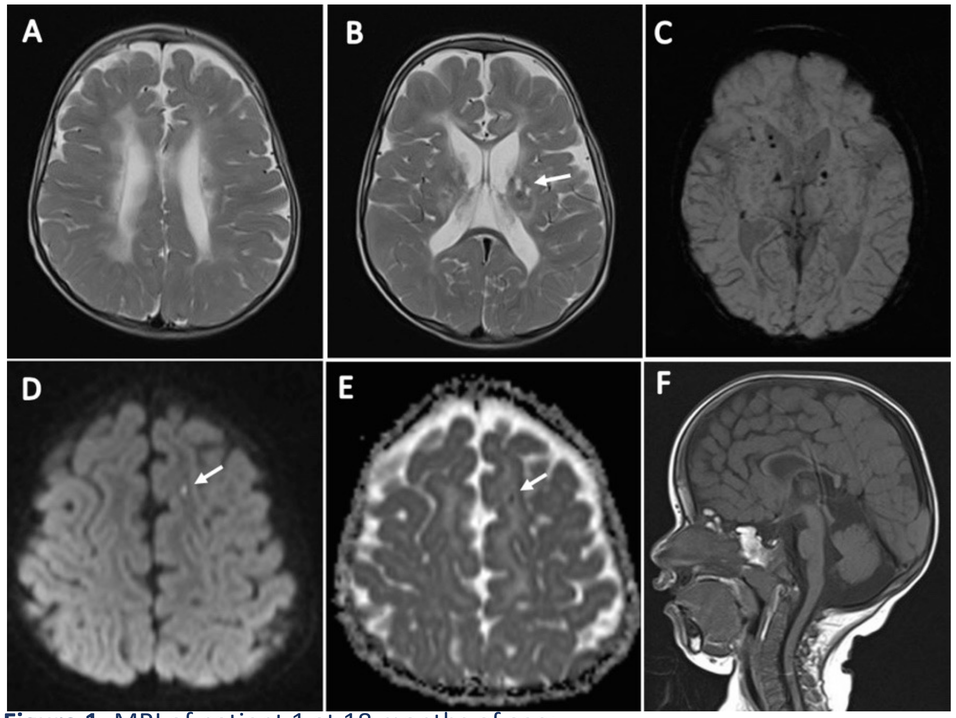

Figure 1. MRI of patient 1 at 18 months of age:

(A) T2 weighted image shows bilateral asymmetric areas of T2 hyperintensities in the periventriateracular white matter.

(B) Focal T2 hyperintense foci in the left basal ganglia and periventricular matter (arrows) that do not show diffusion restriction (not shown here) representing old lacunar infarct.

(C) Maximum intensity projection of susceptibility weighted image shows foci of microhemorrhage in the basal ganglia and white matter.

(D,E) Diffusion weighted image and ADC map demonstrate a tiny acute infarct in the left centrum semiovale.

(F) Diffuse thinning of the corpus callosum is seen is seen on sagittal T1.

Clinical Report

- Neuroimaging of patient 1 is shown (**Figure 1**)
- Biallelic nonsense variants were found in both patients (NM_000435.3:c.2203C>T (p. [Arg735Ter])
- Parents were heterozygous for the same varaint.

Conclusion

- Autosomal recessive *NOTCH3*-related leukodystrophy is usually caused by biallelic null mutations in *NOTCH3* gene.
- The phenotype of biallelic null variants is associated with more severe phenotype compared to the dominantly inherited form of the disease.
- Heterozygous null mutation carriers are most likely unaffected with CADASIL.
- To further understand the heterozygous patients for null mutations, larger longitudinal data is required.

References

1) Pippucci T et al. Homozygous NOTCH 3 null mutation and impaired NOTCH 3 signaling in recessive early-onset arteriopathy and cavitating leukoencephalopathy. EMBO Mol Med 2015; 7:848–58. 10.15252/emmm.201404399.
2) Greisenegger et al. A NOTCH3 homozygous nonsense mutation in familial Sneddon syndrome with pediatric stroke. J Neurol 2021; 268:810–6. 10.1007/s00415-020-10081-5
3) Stellingwerff MD et al. Early-onset vascular leukoencephalopathy caused by bi-allelic NOTCH3 variants. Neuropediatrics 2022; 53:115-21. 10.1055/a-1739-2722