NANS-CDG: delineation of the genetic, biochemical and clinical spectrum.

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Background

Congenital disorders of glycosylation (CDGs) comprise a large group of genetic defects affecting the glycosylation of proteins and/or lipids. NANS-CDG is caused by bi-allelic genetic variants in NANS, encoding an essential enzyme in de novo sialic acid synthesis (1). Sialic acid at the end of glycoconjugates plays a key role in biological processes such as brain and skeletal development (2). In 2016, NANS-CDG was frist described by Van Karnebeek et al. as a human inherited metabolic disease (3). The limited numbers of patients with NANS-CDG have hindered characterization of the phenotypic spectrum associated with NANS variants.

Aim

To delineate the genetic, biochemical and clinical phenotype and assess possible correlations between genotypes, phenotypes, and ManNAc excretion levels.

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References

Acknowledgements
Patients
Families
Clinicians and lab specialists
MetaKids
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Methods

Medical and laboratory records were reviewed with retrospective extraction and analysis of genetic, biochemical and clinical data (2016-2020).

Results

9 NANS-CDG patients (nine families, six countries) referred to the Radboudumc CDG Center of Expertise were included.

Phenotype

Hallmark features include:

- Intellectual developmental disorder (IDD)
- Facial dysmorphisms
- Neurologic impairment
- Short stature
- Skeletal dysplasia
- Short limbs

New features are:

- Ophthalmological abnormalities
- Abnormal septum pellucidum (SP)
- (Progressive) cerebral atrophy and ventricular dilatation
- Gastrointestinal dysfunction
- Thrombocytopenia
- Hypo-LDL

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Figure 1 Brain MRI scans of 1 patient. (D, E) Age 4 days: ventriculomegaly, absence of SP, limited volume of corpus callosum. (F, G) Age 25 months: ventriculomegaly and enlarged subarachnoid space, absence of SP. (H) Age 28 months: severely enlarged ventricles, narrow aqueduct and fourth ventricle.

Figure 2 X-rays of the skeleton of 1 patient at age 4 days. (A) Pelvis: flat acetabula, short femoral necks. (B) Right arm: metaphyseal widening, irregularity. (C) Knee: metaphyseal widening, irregularity in detail.

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Biochemical

↑ Urinary excretion of ManNAc is pathognomonic, the concentrations of which show a positive significant correlation with disease severity.

Figure 3 ManNAc excretion levels in urine (µmol/mmol creatinine, reference: “not detected”) vs. The Nijmegen Pediatric CDG Rating Scale (NPCRS).

Label numbers indicate the patients. □, analyses excluding patient 2; *, significant at the 0.05 level; +, patients harbor the same mutation; ~, in patient 2 (aged 3 months), important developmental milestones are not relevant at this young age, explaining why the clinical severity classification is lower than expected on the basis of ManNAc excretion level; ^, patient is treated with prenatal and postnatal sialic acid.

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Results

Genetic

Eight novel NANS variants were identified. 3 severely affected patients harbored identical pathogenic variants; one was initiated on experimental pre- and postnatal sialic acid therapy. This patient showed better psychomotor development than the other 2.

Figure 3 Gene and protein structure of NANS encoding NANS.

Discussion

↑ ManNac ↗ the more severe the diagnosis

NANS-CDG is a progressive neurometabolic disorder with multi organ involvement

Personalized management includes accurate genetic counseling, and care for GI symptoms, thrombocytopenia and epilepsy, as well as rehabilitation for cognitive and physical impairments

Future directions

Follow-up of experimental sialic acid treatment in 5 patients

More patients ↠ explore genotype-phenotype correlations

Research on sialic acid metabolism ↠ unravel complete pathophysiology

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