Mild cases in Canavan disease

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Background

Canavan disease (CD) is a rare hereditary disease, caused by congenital deficiency of Aspartoacylase (ASPA) due to pathogenic variants in the *ASPA* gene. Typical affected patients show a psychomotor developmental arrest within the first six months of life and progressive macrocephaly. Most patients suffer from severe neurological disabilities, leading to complete helplessness in their first years of infancy (1). Remarkably, a small subgroup of patients remains mildly affected (2, 3, 4), reaching psychomotor developmental milestones such as walking and talking. They often preserve certain abilities over years before experiencing a decline in their functions.

Methods

As part of the research project PeriNAA we present data from a cohort of 48 patients with confirmed diagnosis of CD. Genetic, radiological and clinical information about the courses of the disease, including the Canavan disease rating score (CRDS) (1), was analyzed. Data of milder affected patients (who acquired at least temporary ability to walk with support or speak words) were compared with CD patients suffering from the “typical” form of the disease.

Results

11 patients of the cohort gained the ability to walk with support, whereas only 6 patients learned to walk without support. 10 patients learned to speak at least some words, though only 6 patients reported speaking in sentences. The average CDRS total score in the group that had acquired at least 3 of these 4 milestones (7 patients) was significantly lower than the score of the typical severe cases. In most of these milder cases, the head circumference was mainly within the normal range. Analysis of MRI scans showed representative findings (3), although there were overlaps and inter individual differences in the patterns at the same levels of clinical severity. The majority of clinically milder patients showed compound heterozygosity of pathogenic variants of the *ASPA* gene, carrying at least one variant previously described as associated with a milder course of the disease (2, 4).

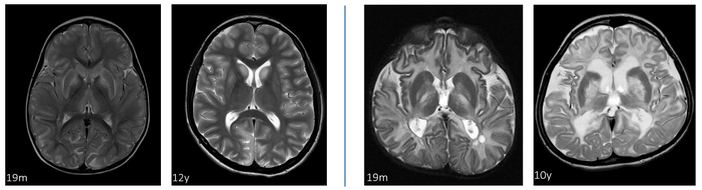

Figure 1. T2-weighted transversal MRI images of mild (left) vs. typical (right) CD patients. Typical cases: caput nucl. caudatus and putamen preserved, i.e. globus pallidus and thalamus (lat.) affected, global atrophy. Milder cases: caput nucl. caudatus, inner thalamus and putamen affected, less abnormal myelination.

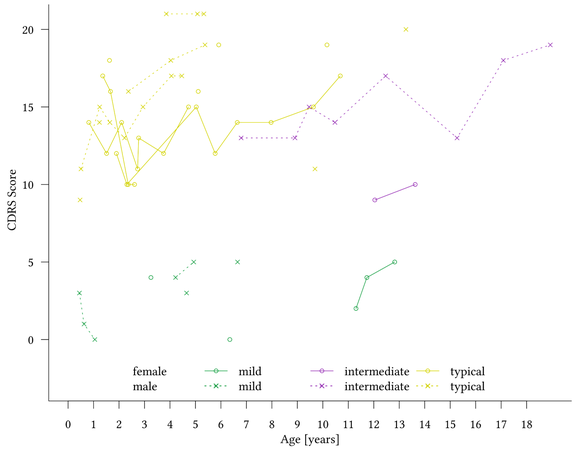

Figure 2. Total values of Canavan Disease Rating Score (CDRS) in the course of disease. Candidates with permanent values < 10 were indicated as mild (green), clinically intermediate cases are shown in purple. (n=23)

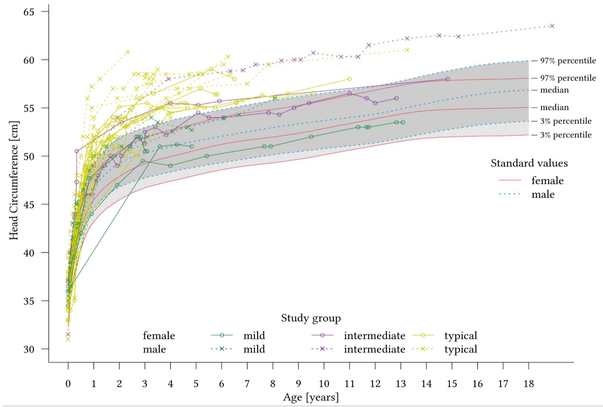

Figure 3. Head circumference in male and female CD patients. Color-coded visualization for different clinical severity levels. Crosses indicate males, circles females. Grey area indicates reference percentiles for head circumference of girls (red) and boys (blue) (Robert-Koch-Institute, KIGGS). (n=44)

Patient \ Ability	Walking with support	Walking w/o support	Speaking words	Speaking sentences
1	yes (t)	no	yes (t)	no
2	yes (t)	no	yes (t)	no
3	yes	no	yes	no
4	yes	no	no	no
5	yes	yes (t)	yes	yes
6	yes	yes	yes	yes
7	yes	yes	yes	yes
8	yes	yes	yes	yes
9	yes	yes	yes	no[a]
10	yes	no	yes	yes
11	yes	yes	yes	yes

Table 1. (a) Ability to walk with/without support and speak words/sentences in the milder patient cohort. None of the other 37 severely affected patients learned to walk or speak. (t) = transient (loss of ability over time), a = age appropiate. (n=48)

Genetic variants	
c.859 G>A	c.914 C>A
c.854 A>C	c.914 C>A
n/a	n/a
c.820 G>A*	c.914 C>A
c.863 A>G	?
c.820 G>A*	c.604 G>C.
c.820 G>A*	c.604 G>C
c.212 G>A *	c.541 C>A
c.212 G>A*	c.914 C>A
c.820 G>A*	c.177 dup.
c.914C>T	c.914C>A

(b) Genetic findings in milder patients. * = variant described in ass. with milder course of CD earlier.

Discussion & Conclusion

Atypical mild courses of Canavan disease share common clinical findings such as the abilities to speak at least some words or walk with support. Head circumference may be elevated or normal. The *ASPA* variant c.820 G>A was found in compound heterozygosity in 4 mildly affected patients, while the variant c.212 G>A was found in 2 patients with a milder course. Mildly affected patients kept the described abilities for different time spans up to the age of 13 years at the last follow up. Patients who only preserved the ability to walk and speak words transiently also showed higher CDRS and larger head circumferences during the course of the disease. MRI scans of mildly affected patients often share common findings such as less abnormal myelination and involvement of nucleus caudatus and putamen.

Head circumference measurements and, particularly, the CDRS appear to reflect the spectrum of CD well. However, due to the small number of patients described so far and the considerable heterogeneity of the group, further data analysis is needed to determine a distinct definition of severity.

Literature: (1) Bley A et al. The natural history of Canavan … Orphanet J Rare Dis 2021 May 19;16(1):227. , **(2)** Tacke U et al. Possible Genotype-Phenotype Correlations in … Neuropediatrics 2005;36: 252 – 255 , **(3)** Yalcinkayya C et al. Atypical MRI Findings in … Neuropediatrics 2005; 36: 336-339 * , **(4)** Janson CG et al. Mild-onset presentation of Canavan's disease … Ann Neurol. 2006 Feb;59(2):428-31. *

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