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Canavan disease: emerging cases in non-Ashkenazi population

Choroba Canavan: występowanie poza społecznością aszkenazyjską

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Canavan disease (CD) is one of leukodystrophies – genetic diseases that typically become evident during the neonatal/infancy period or in childhood, and rarely in adults. The pathological condition is also called Canavan–van Bogaert–Bertrand disease and regarded mainly as an Ashkenazi Jewish genetic disorder. It is an uncommon hereditary disease characterised by the degradation of brain white matter and damage to the myeline sheath.

In 1939, neuropathologist Myrtelle May Moore Canavan first observed and reported a pathological condition involving spongy degeneration of the brain's white matter in affected patients. It was later further characterised by Van Bogaert and Bertrand in 1949, but a major breakthrough in understanding the underlying defects of the disorder came in 1988, when Matalon et al. identified the associated enzyme deficiency.

The central nervous system is the main affected organ, which leads to severe neurological symptoms such as motor function impairment, progressive intellectual disability, and developmental delays. The most frequently observed clinical features include decreased muscle tone, macrocephaly, profound intellectual disability, and optic atrophy. Life expectancy varies but is generally reduced to childhood only, although some individuals may survive into adolescence.

The disorder is caused by mutations in the aspartoacylase (*ASPA*) gene, which results in a lack of aspartoacylase, an enzyme essential for the hydrolysis of N-acetyl aspartic acid (NAA). Genetically, it is an autosomal recessive disorder of the *ASPA* gene, located on chromosome 17p13.2. Mutations in the *ASPA* gene lead to a deficiency of the aspartoacylase enzyme, resulting in the accumulation of N-acetylaspartate (NAA) in the brain, which contributes to the degeneration of the myelin sheath. The E285A mutation is the most common variant and is predominantly found in the Ashkenazi population, while the A305E mutation has been reported in non-Jewish populations. More than 80 mutations in the *ASPA* gene have been identified that correlate with CD (Sistermans et al., 2000). A significant recent review on the topic was published by Grønbæk-Thygesen and Hartmann-Petersen (2024). Tab. 1. lists some of the disease's synonyms.

Earlier studies suggested that the disease is common to the Ashkenazi Jews population (Elpeleg et al., 1994) from Eastern and Central Europe, with an estimated prevalence of 1 in 6,400 to 13,500 individuals in the Ashkenazi Jewish community. Based on the facts, physicians or care providers in developing countries often neglect or ignore the possible occurrence of such diseases in their populations.

To assess awareness of the disease, the authors distributed a questionnaire to 114 health care providers across various cities in the country. Surprisingly, 74% of the respondents were either completely unaware or had only limited information. On the other hand, there is a lack of precise national prevalence data across countries but limited research

Canavan–van Bogaert–Bertrand disease	Infantile Canavan disease
Spongiform leukodystrophy	Neonatal Canavan disease
Spongy disease of white matter	Sporadic form of Canavan disease
Van Bogaert–Bertrand syndrome	Aminoacylase 2 deficiency
Spongy degeneration of the central nervous system	*ASPA* deficiency
Familial form of Canavan disease	ACY2 deficiency
Spongy degeneration of central nervous system	ASP deficiency
Spongy degeneration of white matter in infancy	Deficiency disease, aspartoacylase
Spongy degeneration of the brain	Aspartoacylase deficiency
Spongwy disease of central nervous system	Canavan disease, juvenile
Spongy degeneration of infancy	Juvenile Canavan disease

Tab. 1. Some of the synonyms of CD

has documented cases of Canavan disease in different developing countries like Pakistan, India, China, Japan, Saudi Arabia, Turkey, the United States, Norway, and Sweden. The disorder is expected to be present in other countries as well but is usually ignored due to being considered an Ashkenazi Jews population disease. One of the several reasons for disease prevalence among different ethnicities may be consanguineous marriages, which are more common in developing countries (Ahmad et al., 2015). For instance, about sixty percent marriages in Pakistan has been reported as consanguineous (Iqbal et al., 2022). Similarly, some Middle Eastern countries have reported higher rates of CD due to consanguinity. Singh et al. (2020) screened the carrier rates of CD among 200 different ethnic populations of Asia and found a carrier rate of 1/200. Zhang et al. (2010) reported cases of CD in the Chinese population. Sherazi et al. (2017) reported 2.3% cases of CD in Pakistan from one hospital only during a one-year period. Ozand et al. (1990) identified cases of CD in the non-Jewish population in Saudi Arabia. CD is thought to affect 1 in 40,000 live births in the United States. Olsen et al. (2002) reported cases in Norwegian and Swedish populations. Shaag et al. (1995) identified nine mutations in the *ASPA* gene across 19 non-Jewish populations. However, these data are incomplete and may not accurately represent the true prevalence of the disease in populations outside the Ashkenazi community.

CD can be diagnosed through blood and urine tests for N-acetylaspartic acid, along with brain magnetic resonance imaging (MRI) scans. MRI typically reveals diffuse white matter abnormalities, ventriculomegaly, and demyelination, while other imaging techniques, such as computed tomography, may show white matter hypodensity (Hoshino and Kubota, 2014). Even though advanced treatments such as gene therapy, enzyme replacement therapy, and stem cell therapy are still in experimental stages, they hold a significant potential for improving patient outcomes.

Dispelling myths and addressing misconceptions surrounding CD are paramount for promoting awareness, early diagnosis, and access to care. Genetic factors, such as the degree of consanguinity and the accessibility of genetic screening and diagnostic facilities, impact the occurrence of CD. Prenatal genetic screening for the disease should be implemented and recommended by appropriate authorities. While historically associated with specific populations, CD transcends ethnic boundaries and affects individuals worldwide. Autosomal recessive disorders like CD tend to be more common in populations with higher consanguinity rates, such as in several Middle Eastern and South Asian countries.

Collaborative efforts in research, advocacy, and health care delivery are essential for improving outcomes and enhancing the quality of life for individuals with CD. By testing for known familial mutations, parents can make informed decisions about managing their pregnancy and future reproductive options, allowing for the early detection of CD during pregnancy.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

Author contribution

Original concept of study: ZB, SMN. Collection, recording and/or compilation of data: SMN. Analysis and interpretation of data: SM. Writing of manuscript: ZB, SM. Critical review of manuscript: SMN, SA, SM. Final approval of manuscript: SMN, SM.

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