CASE REPORT

Early diagnosis of Canavan syndrome: how can we get there?

Giuseppe De Bernardo,¹ Maurizio Giordano,² Desiree Sordino,¹ Salvatore Buono³

¹Department of Emergency, NICU, AORN Santobono Pausilipon, Naples, Italy

²Department of Emergency, Federico II University, Naples, Italy

³Department of Neurology, AORN Santobono Pausilipon, Naples, Italy

Correspondence to

Dr Giuseppe De Bernardo, debernardo.giuseppe@alice.it

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SUMMARY

Canavan syndrome is a rare genetic disorder characterised by progressive severe leukodystrophy involving the degeneration of white matter. Currently, there is no effective therapy, but after recent studies using early gene therapy, the outcome has appeared to improve. It is of fundamental importance to recognise signs of neonatal Canavan syndrome early on. We describe a case of neonatal Canavan syndrome in which diagnosis was made only at the fourth month of age.

BACKGROUND

Canavan syndrome (CS) is characterised by gene mutation ASPA located on chromosome 17p13.3. The most frequently observed mutations are point mutations, the p.Glu285Ala and p.Tyr231X. The disease has autosomal recessive transmissibility. The disease presents with non-specific clinical signs at birth, such as macrocephaly, usually during the first month of life, loss of mental and motor milestones, and asymmetry of the palpebral fissure. Currently, there is no effective therapy, but after recent studies using early gene therapy, the outcome has appeared to improve. It is of fundamental importance to recognise neonatal aspecific signs of CS early on.

CASE PRESENTATION

An infant was born at 39 weeks of gestational age, by elective caesarean section, to non-consanguineous parents in a peripheral hospital. Apgar score was 9^I–10^V. The infant was discharged after 48 h. Since birth, asymmetry of the palpebral fissure and difficulties in breastfeeding due to poor sucking and swallowing were noted by the parents (figure 1). The head circumference and body weight percentiles were always >97^o from the first month of life, while the length was normal for age. The infant was admitted to our hospital at fourth month of age for loss of mental and motor milestones, suspected blindness, macrocephaly, loss of eye contact and neck control, and generalised hypertonia.¹ The nuclear magnetic resonance (RMN) was performed after admission, revealing widespread alteration of white matter with symmetrical involvement of the subcortical U-fibres, nucleus, pallidum, thalamus, optic radiations, substantia nigra and brainstem (figure 2). The RMN spectroscopy of semioval centres revealed an increased acid N-acetylaspartate/choline (NAA/Cho) and acid N-acetylaspartate/creatinine ratio, suggesting a CS diagnosis,² which was confirmed through the analysis of the ASPA gene, detecting the mutations p.A305E and p.A7Vdel8_69. We are

Figure 1 Macrocephaly and the asymmetry of the palpebral fissures.

firmly convinced of the possibility of increasing the number of early diagnoses of CS considering the following neonatal signs: progressive macrocephaly already present during the neonatal period and neurological deterioration. The diagnosis should then be confirmed by the increase in urinary NAA concentrations, the increased NAA/Cho ratio detected with RMN spectroscopy of the semioval centres and the genetic test, in order to make improvement of the quality of life possible using early supportive therapy and, in the near future, using experimental gene therapy.³

Figure 2 Globus pallidum (single arrow), thalamus (double arrow) and optic radiations (triple arrow).

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INVESTIGATIONS

- ▶ Urinary NAA concentrations
- ▶ RMN spectroscopy
- ▶ Analysis of the ASPA gene.

DIFFERENTIAL DIAGNOSIS

All leukodystrophies with macrocephalia: glutaric aciduria type 1, deficit of hydroxyglutaric S-hydrogenase, D2-hydroxyglutaric aciduria, Alexander disease, GM2 gangliosidosis.

TREATMENT

Supportive care is currently the only therapy. Recent promising studies on gene therapy demonstrated how the best outcomes were achieved in infants with early diagnosis.

OUTCOME AND FOLLOW-UP

The outcome of infants with CS is characterised by hypotonia during the first month of life, which will change to spasticity and failure to achieve independent sitting, deambulation or speech. Macrocephaly, lack of head control and developmental delay will appear from 3 to 5 months. Follow-up aims to provide adequate nutrition and hydration to prevent infectious diseases. Usually, the final outcome is death within the teenage years.

DISCUSSION

Three other similar cases of neonatal CS are reported in the literature. In those cases, the patients presented with macrocephaly, nystagmus and lack of head control, between 4 and 6 months of life. The analysis of urinary concentration of NAA and RMN spectroscopy of the semioval centres were essential to suspect the diagnosis. Genetic testing confirmed the diagnosis. The only currently available therapy is supportive care. Recently, gene therapy was experimented with, achieving better results when the therapy was started between 0 and 3 months of life. The gene therapy used an adeno-associated viral vector carrying the ASPA gene (AAV2-ASPA). The preliminary results showed a decrease in elevated NAA in the brain and slowed

progression of brain atrophy, with stabilisation of overall clinical status. Thus we highlight the importance of speedy recognition of neonatal specific signs of CS for an early diagnosis of this disease.

Learning points

- ▶ Canavan syndrome is a rare, hypomyelinating genetic disorder, characterised by progressive severe leukodystrophy involving the degeneration of white matter.
- ▶ The mutation of the ASPA gene on Cr 17p13.3, encoding the enzyme aspartoacylase, determines a deficit in the storage of (acid N-acetylaspartate) in the white matter, specifically in astrocytes. Gene therapy is currently the only therapy.
- ▶ Recent clinical trials demonstrated how the best outcomes were achieved in infants with early diagnosis.

Contributors GDB admitted the patient, conceived the work, wrote the first draft of the manuscript and reviewed the final draft. MG collected the data and participated in writing the first draft of the manuscript. DS participated in writing the first draft of the manuscript. SB helped in making the diagnosis and supervised the work.

Competing interests None declared.

Patient consent Obtained.

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