CURIOUS CASES OF CANAVAN DISEASE

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INTRODUCTION

- Canavan disease- Severe progressive leukodystrophy
- Caused by aspartoacylase (ASPA) Deficiency
- Due to mutation in ASPA gene, on chromosome 17 (17p13.2), with an autosomal recessive inheritance
- The typical clinical features:

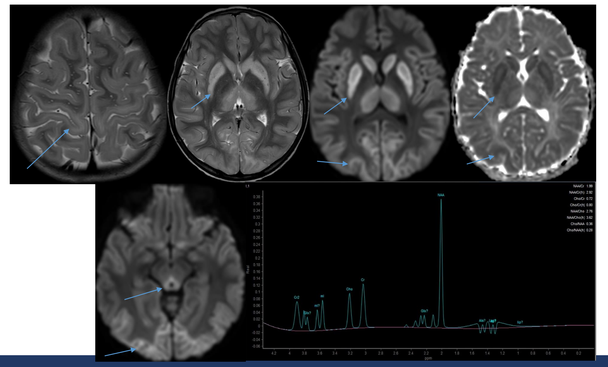
1. Global developmental delay apparent by the age of three to five months
2. Hypotonia
3. Macrocephaly
4. Optic atrophy.

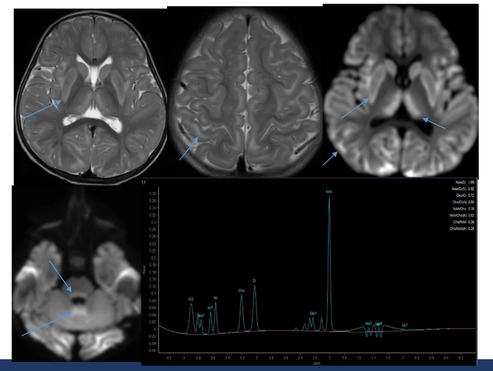
- The characteristic MRI findings- Diffuse, symmetrical white matter degeneration in the subcortical areas, with bilateral involvement of the globus pallidus with magnetic resonance spectroscopy of the brain suggestive of an increase in the concentration of *N*-acetylaspartic acid (NAA).
- We present two phenotypically different cases of Canavan disease with distinct neuroimaging picture.

CONFIRMATORY TEST

CASE 1 : WES-	*CASE 2- Urine*
ASPA gene - compound heterozygous Autosomal recessive Likely pathogenic ***1. c.782T>A, exon 6, missense variant, VUS 2. C.306delA, exon 2, frameshift variant, LP***	***GCMS- 31.7% peak (upper limit 3.7%) 8.59 fold (mild) elevation of N acetyl aspartate.***

Feature	Case 1	Case 2
Demography	8 years old boy	2 years old girl
Consanguinity	Yes, 3rd degree	Yes, 3rd degree
Birth history	Normal	Normal
Developmental history	Global developmental delay (neck holding 6 months, stand 5 years, walking 6 years, bisyllables 1.5 years)	Developmental delay (stand 18 months)
Chief complaints	Progressive ataxia, tremors, slurring of speech since 3 years of age	Tremulousness and abnormal eye movements.
Presentation	Normocephaly (51 cm), spasticity, brisk reflexes, cerebellar signs, ataxic gait	Normal head circumference for age (47 cm), Spasticity, brisk reflexes
Ophthal	Normal fundus	Alternating esotropia, normal fundus
Metabolic workup	Normal except, serum lactate- 2.95 (UL 1.8)	Normal VBG, lactate, NH3
Other	Normal AFP and NCV	-
MRI brain	Bilateral symmetrical areas of T2 and FLAIR hyperintesity in corpus striatum, medial thalami, periaqueductal gray matter, dentate nuclei, superior vermis, inferomedial aspect of cerebellar hemispheres and dorsal brainstem. Restricted diffusion in subcortical U fibers, deep grey nuclei, brainstem, cerebellum, *giving '**rim sign**' in basal ganglia.*	Bilateral T2 and FLAIR hyperintensity with restricted diffusion in sub cortical white matter, deep cerebellar white matter inferomedial and posterior aspect, dorsomedial thalami and margins of corpus striatum (caudate and putamen) Restricted diffusion also in dorsal brainstem including inferior colliculus and superior vermis.
MRS	***very large NAA peak***. NAA: creatinine (h) ratio (2.92)- mild elevation	***High NAA peak*** NAA: creatinine (h) ratio (1.97)





DISCUSSION

- Three different forms of CD- infantile (most common), early infantile form and juvenile form.
- Juvenile- symptoms after the age of 5 years- cerebellar ataxia, spasticity, and loss of vision and death occurs in late adolescence.
- In mild cases of Canavan disease, the MRI involves predominantly he basal ganglia, mimicking mitochondrial diseases.
- Atypical MRI findings- the absence of prominent leukodystrophy with selective involvement of the U-fibers only and presence of hyperintense signal of putamen, globus pallidus, the head of the caudate nuclei, and dentate nuclei on the T2-weighted MR images have been reported previously.
- Our patients did not have the usual clinical features of macrocephaly, vision and cognitive impairment.
- In our case 1 mitochondrial disorder was suspected in view of elevated serum lactate, but a clinic-radiological diagnosis was made after MRS suggestive of atypical presentation Canavan disease.

REFERNCES

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CONCLUSION

These cases emphasize on the phenotypic variability and evolving spectrum in neurodegenerative disorders.