Aminoacylase-1 deficiency , a clinical perspective

Nazreen K Jaman[1]; Steve Krywawych[1];
Paul Gissen [2],James Davison [2;] Great Ormond Street Hospital NHS Foundation Trust , London UK

Great Ormond Street Hospital for Children
NHS Foundation Trust

AIM

The aim of the current study was to review the clinical and Neuroradiological features of a single-centre cohort of patients with ACY1D.

Figure :6
UOA chromatography patient 3

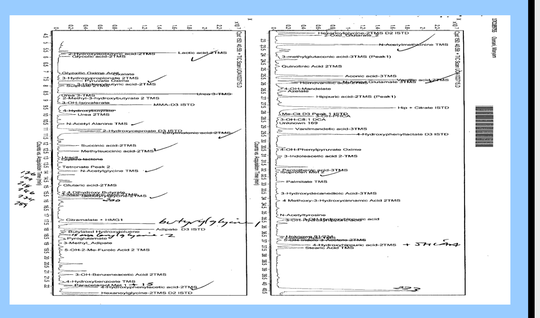
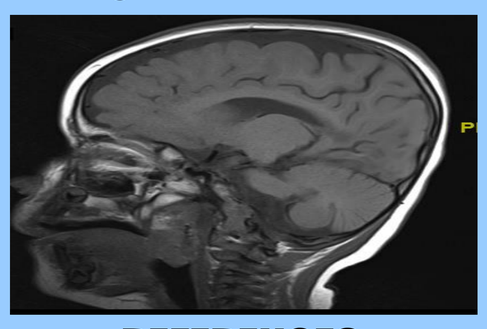


Fig 5:Pt 1 MRI Brain



REFERENCES

1. Ferri L, Funghini S, Fioravanti A, Biondi EG, la Marca G, Guerrini R, Donati MA, Morrone A. Aminoacylase I deficiency due to ACY1 mRNA exon skipping. Clin Genet. 2014 Oct;86(4):367-72. doi: 10.1111/cge.12297. Epub 2013 Nov 18. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24117009
2. Engelke UF, Sass JO, Van Coster RN, Gerlo E, Olbrich H, Krywawych S, Calvin J, Hart C, Omran H, Wevers RA. NMR spectroscopy of aminoacylase 1 deficiency, a novel inborn error of metabolism. NMR Biomed. 2008 Feb;21(2):138-47. Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17516490

CONTACT

Name : Nazreen B Kamarus Jaman
Hospital: Great Ormond Street Hospital NHS Foundation Trust, London UK“
Email: Nazreen.kamarusjaman @ gosh.nhs.uk
Web: www.gosh.nhs.uk

***No conflicts of interest**

BACKGROUND

Aminoacylase 1 deficiency (ACY1D; MIM #609924) is an autosomal recessive disorder biochemically characterized by increased urinary excretion of specific N-acetyl amino acids, caused by biallelic mutations in ACY1 resulting in deficiency of aminoacylase 1 (EC3.5.1.14). Aminoacylase 1 normally functions to deacylate L-amino acids, removing the acyl group, during protein catabolism. Clinically, patients with ACY1D may have neurological problems with a wide variation in the pattern and severity of signs and symptoms. Individuals with this condition typically have delayed development of mental and motor skills (psychomotor delay) and may have movement problems, hypotonia and seizures.

METHODS

This retrospective case note review was conducted in a single metabolic center at a tertiary care hospital in the UK. Clinical, biochemical, molecular genetic and neuro-imaging parameters were gathered from the clinical records, with a focus on the neurologic symptoms and signs.

Fig (1-5) Axial MRI brain images

Fig 1(Pt 1)

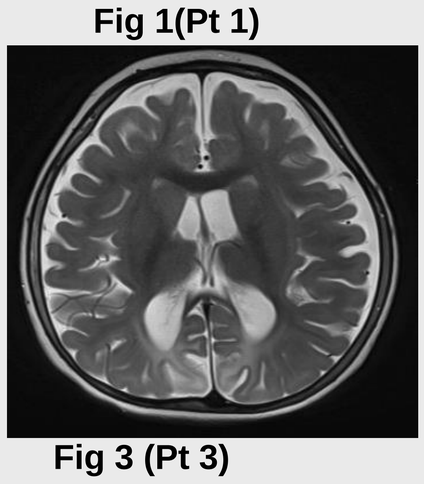


Fig 2 (Pt 1)

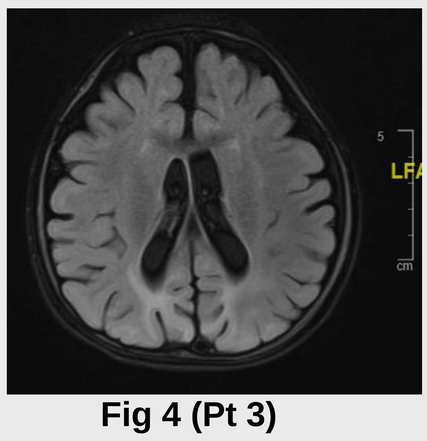


Fig 3 (Pt 3)

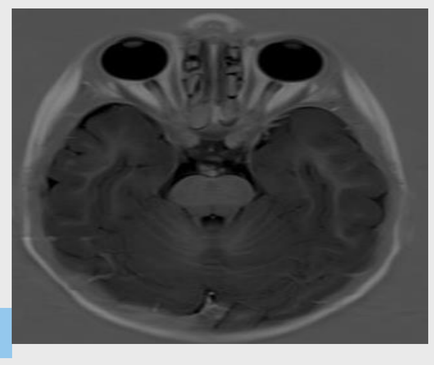


Fig 4 (Pt 3)

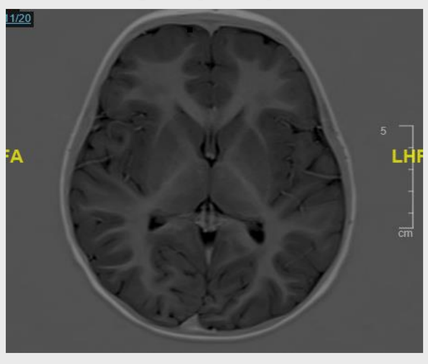


Table : Hypomyelinating neuropathy

Patient	Age diagnosis (yr)	Urine organic acid abnormality	ACY1	Developmental delay?	Hypotonia	Seizures	Neurological Examination findings	MRI Brain features	Notes
1	4 yrs	Mildly raised N-acetylalanine and N-acetylglycine with no increase in N-acetylglutamate, N-acetyltyrosine, N-acetylglycine or N-acetylmethionine - this is supportive of a disturbance in aminoacylase 1 activity	homozygous c.95-2A>G: all bioinformatic tools predict splice acceptor site affected, variant not in databases, class 5, clearly pathogenic.	Yes	Yes	Yes	-	striking volume loss with gliosisin both occipital corticesMore generalised prominence of both cerebral hemispheres.	
2	3 yrs app.	Moderately raised N-acetylalanine and N-acetylglutamate, N-acetyltyrosine, N-acetylglycine - ? disturbed aminoacylase 1 activity	NA	Yes	Yes	No	Sensory neuropathy. Nerve conduction study: no sensory response obtained from the leg/arm,	non-specific ventricular prominence only. EMG: no twitch,continued to show fibrillation potentials.	-Mild congenital Icthyosis.
3	3 yrs	Raised N-acetyl amino acids (N-acetyl alanine, N-acetyl glycine, N-acetyl methionine	c.1057C>T, p.Arg353Cys homozygous	Yes	Yes	No	Motor incordination unsteadiness. -Delayed speech.	Normal	Also SCAD deficiency
4	2 yrs	Moderately raised N-acetylmethionine, N-acetylglutamate, N-acetylglycine and N-acetylalanine - ?	NA	NA	NA	NA	NA	NA	

RESULTS

Four patients were identified, 3 females (current age 4-17 years) and one male (7 years). Diagnosis of ACY1D was based on biochemical findings (4/4) with raised N-acetyl amino acids consistent with deceased/ absent aminoacylase 1 deficiency. Molecular genetic analysis of *ACY1* were available in 2 patients who had homozygous pathogenic variant (see table), 1 of whom also had a biochemical and genetic diagnosis of short chain acylCoA dehydrogenase deficiency (SCAD).

DISCUSSION

Interestingly, most of our patients had neurologic symptoms with different phenotypes involving Global developmental delay, seizures, hypotonic and speech delay. Although the results were shown different phenotypic presentation from four patients, it is worth considering enzymatic analysis for Aminoacylase deficiency along with genetic testing for such patients with complex phenotype. This study identified different phenotypic presentation in four unrelated patients widening the here-to described phenotypic spectrum. Urine organic acid analysis in patients with undiagnosed disorders with neurological phenotype it useful in identifying a range of neurometabolic disorders, and subsequent enzymatic analysis or molecular genetics is important.