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Acute myeloneuropathy due to Glutaric aciduria-1: Expanding the phenotypic spectrum

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ABSTRACT

Glutaric aciduria type-1 (GA-1) is a rare metabolic disorder due to mutation in *GCDH* gene resulting in varied clinical manifestations. Here we report a case of late-onset GA-1 with acute myelo-neuropathy and chronic renal failure. Institutional ethics committee approval was obtained and genetic analysis was done by clinical exome sequencing. Here we present 19 year-old-adolescent male with chronic renal disease for 2 years presented with 5 months history of sudden onset weakness of proximal and distal lower limbs and bladder retention. This was preceded by recurrent episodes of vomiting. On clinical examination he had features of myeloneuropathy. Laboratory evaluation showed significant elevation of blood glutaryl carnitine with very low free carnitine, while extensive white matter signal changes with diffusion restriction, subependymal nodules and involvement of internal capsule were evidenced on brain magnetic resonance imaging. Diagnosis was confirmed by clinical exome sequencing which showed a pathogenic homozygous missense mutation in exon 11 of *GCDH* gene (c .120 C > T, p.His403Tyr). This report expands phenotypic spectrum of GA-1 to include late onset acute myelo-neuropathy with chronic renal failure. A high index of suspicion is required since early treatment might decelerate further disease progression.

Background

Organic acidurias (OADs) are a group of inherited metabolic disorders with a broad spectrum of manifestations, due to involvement of intermediary metabolic pathways. Glutaric aciduria is a type of OAD with autosomal recessive inheritance, and consists

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Table 1
Laboratory investigations of the patient.

S.No	Laboratory tests	Patient values	Normal values
1	Hemoglobin (g/dl)	6.6	11 - 14
2	Total leucocyte count (μL)	35700	5000 - 15000
3	Platelet count (μL)	683000	200000 - 450000
4	Serum sodium (μmol/L)	129.9	136 - 146
5	Serum potassium (μmol/L)	4.5	3.5 – 5.1
6	Serum urea (mg/dl)	121	10.8 – 38.4
7	Serum creatinine (mg/dl)	4.0	0.5 – 1.2
8	Blood random blood glucose (mg/dl)	96	70 −100
9	Plasma Lactate (mg/dl)	36.8	4.5 - 20
10	Plasma Ammonia (μmol/L)	66	16 - 60
11	Blood Vitamin B12 (pg/ml)	2000	197 - 771
12	Serum Homocysteine (μmol/L)	9.8	< 15
13	Glutarylcarnitine/3-OH-hexanoylcarnitine, C5-DC/C6OH (μmol/L)	48.68	0.00 −0.38

of three forms. Glutaric aciduria type 1 (GA-1) is the most common form and is primarily a neurological disorder [1]. The phenotypic presentation extends from frequent infantile onset to less obvious late onset types. The most common presentation is acute metabolic crisis in children followed by progressive extrapyramidal features [2]. There are very few cases of late onset GA-1 reported till date. Here we present a novel clinical presentation of GA-1. This is a clinical report of an adolescent male evaluated during the year 2020. Institutional ethics committee approval was obtained for the study and publication. Data pertaining to the patient were collected from the medical records. Genetic testing was performed by clinical exome sequencing.

Case presentation

A 19 year-old- adolescent male, without significant family history, born healthy to non-consanguineous parents presented with a 5 months history of sudden onset weakness of proximal and distal lower limbs which developed over few minutes, associated with acute bladder retention. There was history of multiple episodes of vomiting prior to symptom onset. He did not have cranial nerve involvement, cognitive or behavioural disorders. He had a 2 years history of chronic renal disease requiring monthly hemodialysis without any other co-morbidities. On clinical examination, the patient was severely emaciated with mild facial weakness, atrophy of proximal and distal lower limbs along with knee and ankle contractures. Muscle strength evaluation showed Medical Research Council (MRC) grade of 3 at shoulder, 4 at elbow and wrist, 1 in the lower limbs. There was patchy sensory loss in the L2-L3 dermatomal distribution. All tendon reflexes were absent with equivocal plantar response. Based on clinical examination, diagnosis of myeloneuropathy was considered. In view of contractures and atrophy of lower limb muscles, the possibility of long standing inherited/ metabolic etiologies than autoimmune or demyelinating causes were first included in the differential diagnosis. The baseline blood investigations are shown in Table 1. Tandem mass spectrometric analysis of blood carnitines showed significant elevation of glutaryl carnitine (C5DC), with very low free carnitine level. Ultrasound of abdomen and pelvis showed bilateral gross hydro-uretero-nephrosis (grade-4). Nerve conduction studies showed demyelinating sensorimotor neuropathy with secondary axonal changes (Table 2). Further, Brain MRI showed bilateral symmetrical white matter hyperintensities with diffusion restriction, subependymal nodules and involvement of internal capsule (Fig. 1). Spine MRI was normal. Whole exome sequencing was then performed showing a pathogenic variant, a homozygous missense mutation in exon 11 of *GCDH* gene (c .1207 C > T, p.His403Tyr), which confirmed the diagnosis of Glutaric aciduria type I. This missense variant in *GCDH* (NM_000159.3):c .1207 C > T (p.His403Tyr) has been previously reported in Clinvar as likely pathogenic/pathogenic in two patients with Glutaric aciduria Type 1 [3,4]. The p.His403Tyr change is not reported in control population databases like gnomAD and 1 kG (1000 Genomes project). Moreover p.His403Tyr change is highly conserved across all species. Additionally, the clinical phenotype of the proband matches completely with the disorder caused by pathogenic mutation in *GCDH* gene. For these reasons, this variant has been classified as pathogenic (American College of Medical Genetics – ACMG guidelines). Patient was given a trial of treatment with diet low in lysine and tryptophan along with oral carnitine 1 g/day (25 mg/kg/day) and riboflavin 400 mg/day (10 mg/kg/day). On reviewing the patient after 6 months, clinical evaluation showed no significant improvement in limb weakness and he continued to be in bedbound state.

Table 2
Nerve conduction study of the patient.

Nerve	Distal/ proximal latency (ms)	Distal/ proximal CMAP amplitude (mv)	Conduction velocity (m/s)	Sensory Latency (ms)	SNAP amplitude (μV)
Median	8.9/17.8	3.2/1.8	26.6	4.0	3.0
Ulnar	5.9/21.6	2.1/1.4	16.6	4.4	2.3
Radial	4.7/10.2	2.2/1.3	25.5	2.7	6.9
Lower limb CMAP and SNAP	Absent	Absent	Absent	Absent	Absent

Footnotes: CMAP- Compound Muscle Action Potential, SNAP- Sensory Nerve Action Potential, ms – Milliseconds, mv – Millivolts, m/s – Meters per second, μV - Microvolts

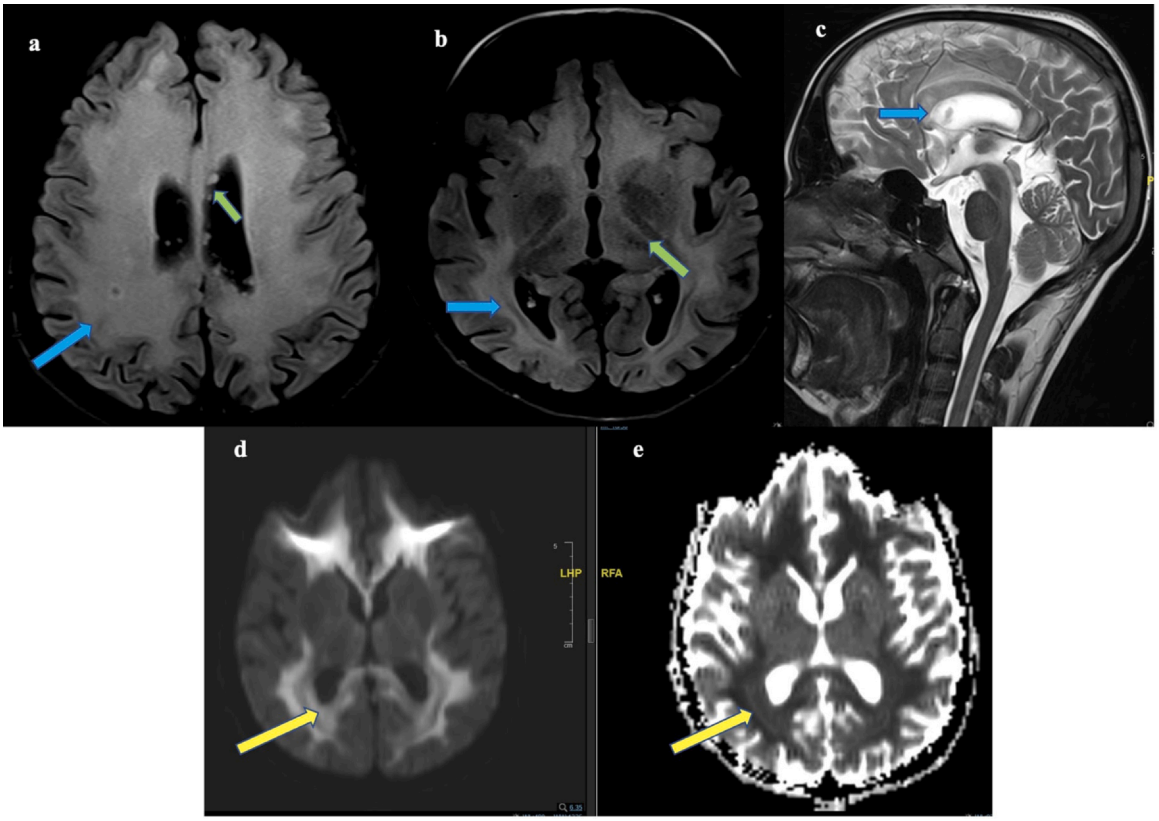

Fig. 1. Brain MRI of the patient. a – Confluent T2/FLAIR hyperintensity is noted in deep white matter of bilateral cerebral hemisphere, with few areas of relative sparing of subcortical U fibers and periventricular white matter predominantly along atria and occipital horns (blue arrow). Few subependymal nodules noted along body of bilateral lateral ventricle (green arrow). b - T2/FLAIR hyperintensity predominantly along atria and occipital horns with sparing of periventricular white matter (blue arrow). Involvement of posterior limbs of bilateral internal capsule along the outer margins (green arrow). c - T2W - involvement of corpus callosum with heterogeneous signal intensity (blue arrow). d – Diffusion restriction in DWI and e – ADC sequences (yellow arrows).

Discussion and conclusions

Glutaric aciduria type-1 is a rare metabolic disorder due to mutation in *GCDH* gene on chromosome 19p13.2, with only over 500 cases reported till date [2]. The defect affects the metabolism and degradation of L-lysine, L-hydroxylysine and L-tryptophan. This results in accumulation of glutaric acid and 3-hydroxyglutaric acid in blood, cerebrospinal fluid and other tissues causing varied manifestations [5]. Infantile onset GA-1 has characteristic acute metabolic crisis with bilateral striatal injury, followed by progressive complex movement disorders [6]. Late onset GA-1 has symptoms after the age of 6 years. There are very few cases of late onset GA-1 reported, and the major manifestations in this group includes chronic headache, epilepsy, tremor and dementia [7–9]. Herkovitz et al., reported a case of late onset (second decade) chronic, very slowly progressive peripheral neuropathy along with subependymal mass lesions and cognitive impairment [10]. Genetic analysis showed missense variation in exon 4 of *GCDH* gene leading to p.Gly101Arg change which resides in the N-terminal region of alpha helical domain of GCDH protein. Similarly, our patient also had onset in the second decade of life. However, he had acute myeloneuropathy with maximal deficit at onset and missense variant p.His403Tyr involving the C-terminal region of alpha helical domain of GCDH protein. Such alteration affects the core protein resulting in misfolding, which may explain the severe involvement in our patient. The proposed mechanism of neuropathy is failure to utilize long chain fatty acids due to secondary carnitine deficiency in GA-1 [11]. Myelopathy has not been reported so far. Our patient had chronic renal failure requiring maintenance hemodialysis with onset in his second decade of life. Du Moulin et al., have described the possible pathomechanisms based on previous reported cases of GA-1 with renal involvement [12]. Most of these are case reports of patients with acute renal failure presenting in the first decade of life. However, chronic renal failure was reported in about 20–25 % of adult patients with GA-1 by Keolker et al., who also noted that occurrence of chronic renal disease was independent of high (as in the case of our patient) or low excretors of urinary glutaric acid [13]. Accumulation of glutaric acid metabolites in the proximal renal tubules results in impairment of mitochondrial function and renal failure [14]. Elevated glutaric acid (GA), 3-hydroxyglutaric acid (3-OH-GA), glutaconic acid and glutarylcarnitine (C5DC) (including C5DC/C8 ratio and C5DC/C16 ratio) in various body fluids such as urine, plasma, cerebro spinal fluid and tissues can be detected by gas chromatography/mass spectrometry (GC/MS) or tandem mass spectrometry (MS/MS) [15,16]. Other non-specific laboratory findings include ketoacidosis, hyperammonemia, and deranged liver function tests based on clinical features [15]. The classical imaging findings in infantile GA-1 are

bilateral symmetric CSF space enlargement along temporal fossa and sylvian fissures, subdural hematomas and signal changes in white matter and basal ganglia. The most common MRI finding in late onset cases is frontotemporal hypoplasia as noted in infantile cases. However, the subcortical white matter hyperintensities increase with age and are more commonly observed in late onset cases. Notably the presence of subependymal nodules along the walls of lateral ventricle is a useful imaging marker for the diagnosis of GA-1 [17]. Our patient showed extensive subcortical white matter changes with widespread diffusion restriction, which is rarely reported in late onset GA-1. The presence of few subependymal nodules in lateral ventricle along the ventricular wall led to the suspicion of GA-1 in our patient. A neuroimaging study done by Boy N et al., in 8 late-onset GA-1 patients showed that the most common imaging findings were frontotemporal hypoplasia (FTH) and periventricular white matter changes of the frontal and parietal regions, while pallidal and dentate nucleus hyperintensity were noted only in a few patients [7]. However, our patient did not have FTH, and showed conspicuous sparing of the periventricular white matter without involvement of grey matter. Also the involvement of corpus callosum is rarely reported [5]. The involvement of the internal capsule noted in our patient is a novel finding.

GCDH gene encodes flavin adenine dinucleotide dependent mitochondrial matrix protein which oxidises and decarboxylates glutaryl CoA. Most of the *GCDH* variants are due to missense mutation affecting the stability of this enzyme complex and disrupting mitochondrial function [5]. Our patient also had a missense variant – c .120 C > T (p.His403Tyr). This mutation has been previously first reported by Wang Q et al., [3] in a Chinese cohort followed by Tamhankar PM et al., [4] in an Indian cohort. Both of the above reported patients had early onset of symptoms in the first decade of life, with acute encephalopathic crisis followed by extrapyramidal features. In contrast, in the current study our patient had late onset of symptoms in the second decade, with renal involvement followed by acute myeloneuropathy being a novel presentation. Though the variant c .120 C > T (p.His403Tyr) is a high excretor form, the late-onset symptoms in our patient may be due to other environmental/ dietary or epigenetic factors which requires to be elucidated. GA-1 has been enclosed in many national newborn screening (NBS) panels including many developed countries of European union and Switzerland, as C5DC can be detected in dried blood spot (DBS) by MS/MS method and early neuroprotective metabolic treatment can be instituted. Genetic analysis by exome sequencing confirms positive NBS and aids both in the diagnostic confirmation and in the identification of asymptomatic carriers in the family, allowing thus appropriate counselling to the parents (including recurrence risk) for primary and secondary prevention of the disorder [18,19]. Our report expands the the phenotypic spectrum of the disease, including late onset myeloneuropathy and chronic renal failure, whose variability may also be dependent on epigenetic and environmental factors [20–25]. Such findings may also be useful to achieve genotype-phenotype correlations. The major aim of NBS in GA-1 is to prevent irreversible striatal injury which occurs during the first 6 years of life called the 'window of vulnerability' [16]. There is a need for a multidisciplinary approach with an important role for pediatricians in the early identification and institution of appropriate management of these patients [26]. The treatment strategy for GA-1 is the combined metabolic management which includes intermittent intensified emergency treatment and maintenance therapy with low lysine diet/ oral carnitine supplementation which has to be started immediately at diagnosis. Previous guidelines have shown oral riboflavin has some benefits [5], but current recommendations report no standardized protocol exists for its utility [16]. However, in cases with late onset and atypical features as noted in the current study, the efficacy of the above treatment is not clear as the period of vulnerability had ended and response of extracerebral manifestations is doubtful. The poor response to the supportive treatment as seen in the present late-onset case confirms the need for prompt identification of the disease to provide a significant benefit in slowing the adverse evolution of the disease, in which therapy has been started long after the symptoms onset.

List of abbreviations

GA-1 - Glutaric aciduria type-1, OADs - Organic acidurias, MRC - Medical Research Council, ACMG - American College of Medical Genetics, FTH - Frontotemporal hypoplasia, C5DC – glutarylcarnitine.

Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Institutional Ethics Committee of National Institute of Mental Health and Neuro Sciences (NIMHANS), Bengaluru, India (Date: 8/8/22, No: NIMH/DO/(BS&NS)2022). Informed consent was obtained from patient and his parents.

Authors' Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by DB, GA, DDSA, AM, TAS, KP, BSS, TJ, SBS, SN, PR, RMC, RY, RC, SV, AN. The first draft of the manuscript was written by DB and all authors commented on previous versions of the manuscript. All authors have read and approved the final manuscript.

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Data availability

Data is available on reasonable request from the corresponding author.

Declaration of Competing Interest

The authors have no relevant financial or non-financial interests to disclose.

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Consent for publication

The authors also affirm that patient and his parents provided informed consent for publication of the images in Fig. 1.

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