Glutaric Aciduria Type 1, a treatable metabolic cause for developmental regression.

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- PANDA Webinar

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Finding a cause for developmental delay

- depends on a well developed system of health
- Surveillance programs
- Parents, GPs, allied health practitioners

- Importance of detecting a cause
  - Accurate counselling
  - Recurrence risk
  - Specific treatment can be used
  - Metabolic decompensation can be avoided

- History, examination, laboratory investigations

Cause may not always be obvious

Gold standards : MRIs/ genetics

- ? How intensively should one investigate for an error in metabolism

Overview of a treatable metabolic cause for developmental delay

- Case studies
- Overview of Glutaric Aciduria Type 1
- Literature

A tele consult during Covid 19

- MDT : Neurology, Development, Dietician and both parents

A family referred for follow up:

- 3 siblings - 6 years
  - 4 years
  - 2 years 6 months
- Different developmental trajectories

- Second child presented first

Second child

Now 4 year old boy

Uneventful birth

No family history

Dyskinesia in mid infancy

U OA: low excreta
GCDH gene mutation

Meds : Carnitine bd
Diet : Maximate (Lysine free, low tryptophan , essential amino acid)

Parents prepared for metabolic crisis

Previous 3 months : No infections, no crisis, dyskinesia was not worsening, no pain, receiving therapy

Clinically ‘ interview‘ :Weight was 40 lb + 18.1 kg

Developmental : Moderate Global Developmental delay

GM : Crawling, starting to climb
starting to use a walker

FM : Using both hands
Completing arts and crafts

Speech : Receptive : Understanding of words and obeyed simple commands
Expressive : 2 words together, improving in number of words, slurred

Personal : Toilet training, starting to be dry at night

Social : engaging with is siblings. They included him but he wasn’t leading in play.

Behaviour : Fewer tantrums, easier to control.

Therapy : Occupational Therapy and Speech therapy, weekly, no reports

Siblings with confirmed GCDH mutations

First child	Index Patient	Third child
6 years girl	4 years	2 years 6 months
Screened after her brother's diagnosis before 3 years of age		Screened at birth
Low excreta		
No Neurological fallout		Developmentally advanced
No therapies		
Carnitine and Lysine free diet		Started on Carnitine and Lysine free diet early
Grade R Enjoys school No challenges from the teacher reports		

Wellness Laboratory investigations :

FBC, Na, K, U, Cr, Alb, CMP

Carnitine within range

Tryptophan was normal

Lysine was low normal

Plan on returning home and were referred back to their primary paediatricians

- My previous experience of GA T1 :

Severe to profound GDD in metabolic crisis

- What is possible in South African…

13 year old boy

at 8 months he presented with gastroenteritis

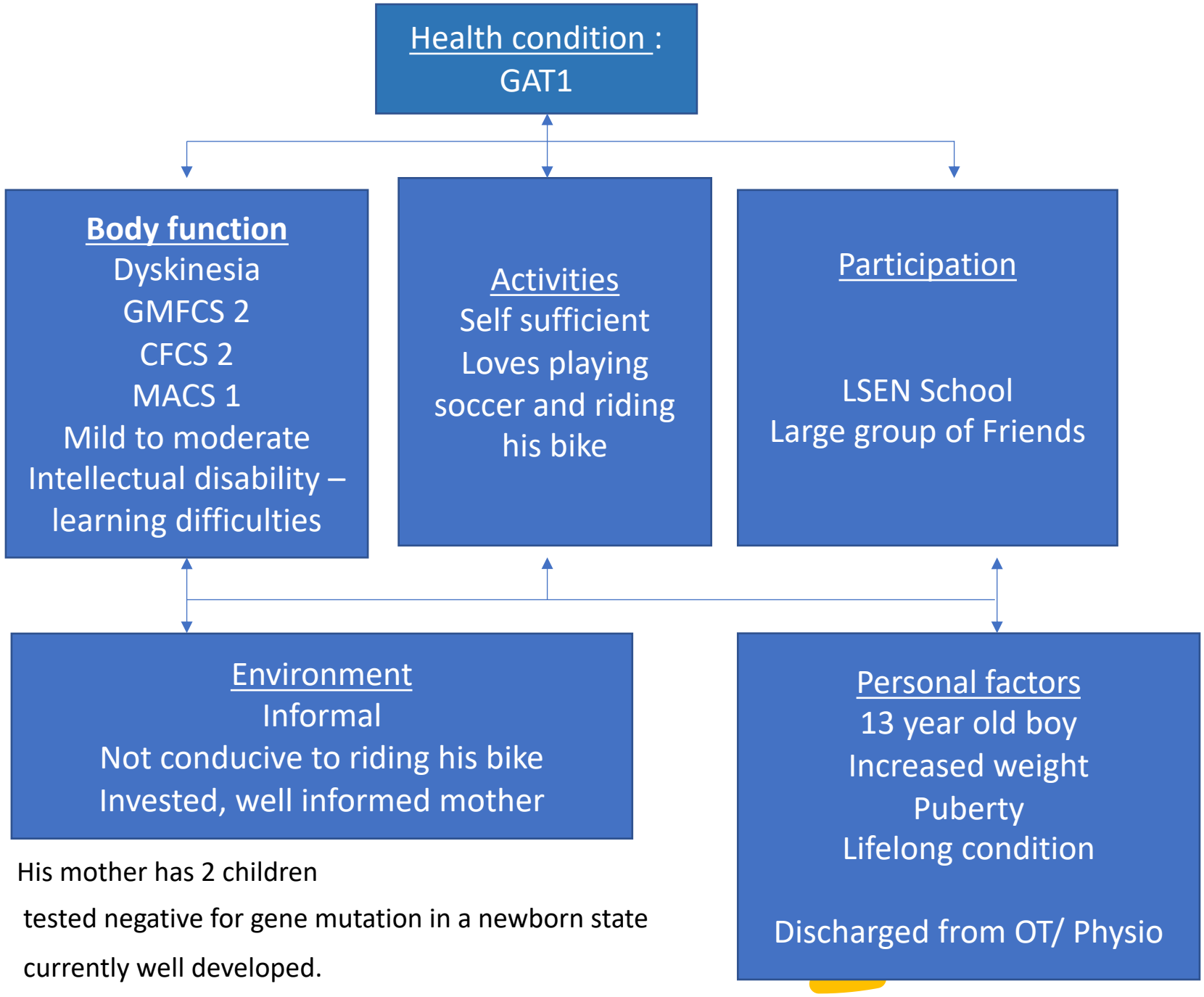
Motor regression prompted a metabolic work up

UOA + Genetics confirmed GAT1

Placed on a low protein diet and L carnitine

A few admissions in metabolic crisis and received emergency treatment

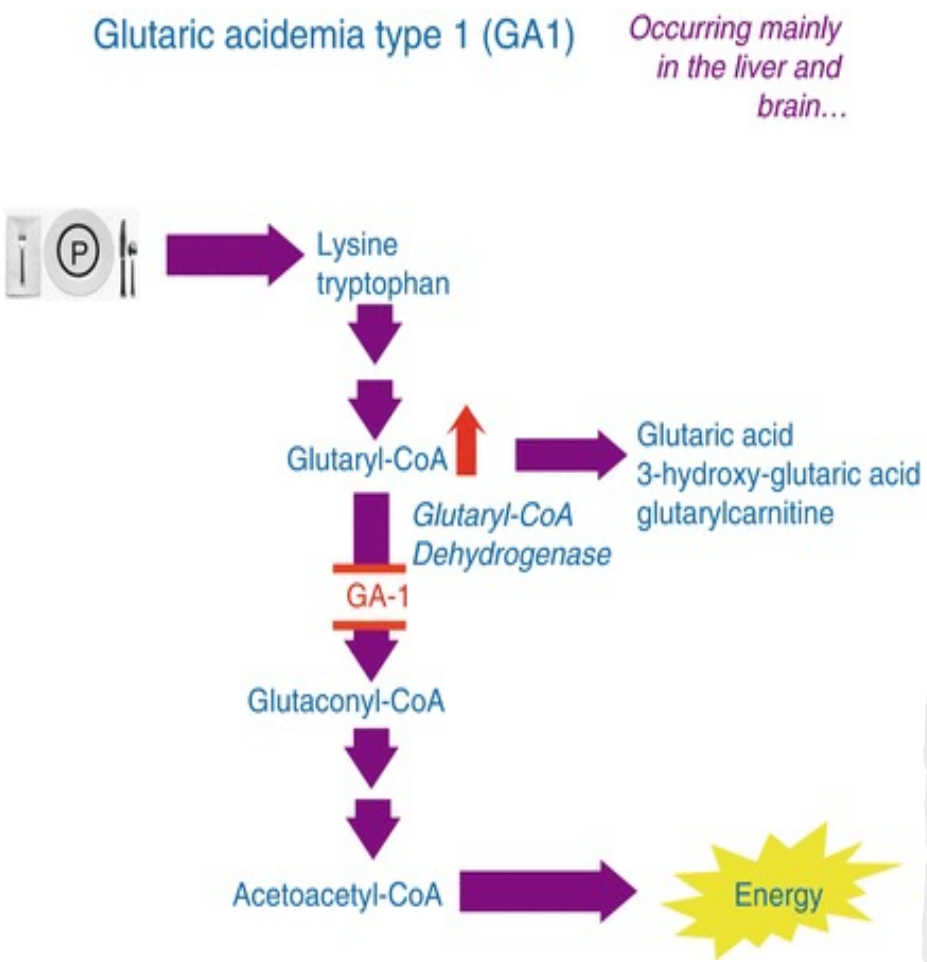
Recent URTI , no crisis



- His mother has 2 children
- tested negative for gene mutation in a newborn state
- currently well developed.

Glutaric aciduria Type 1,

Is a treatable metabolic condition in developmental regression



- Autosomal recessive
- Organic cerebral acidemias
- Affects males and females equally

- caused by a deficiency or absence of the mitochondrial enzyme

  glutaryl-CoA dehydrogenase (GCDH).
- enzyme is responsible for metabolizing the amino acids
  - lysine, hydroxylysine, and tryptophan.

- Defects results in increased concentrations of potentially neurotoxic metabolites
  - glutaric acid (GA),
  - 3-hydroxy glutaric acid (3-OH-GA)
  - glutaconic acid

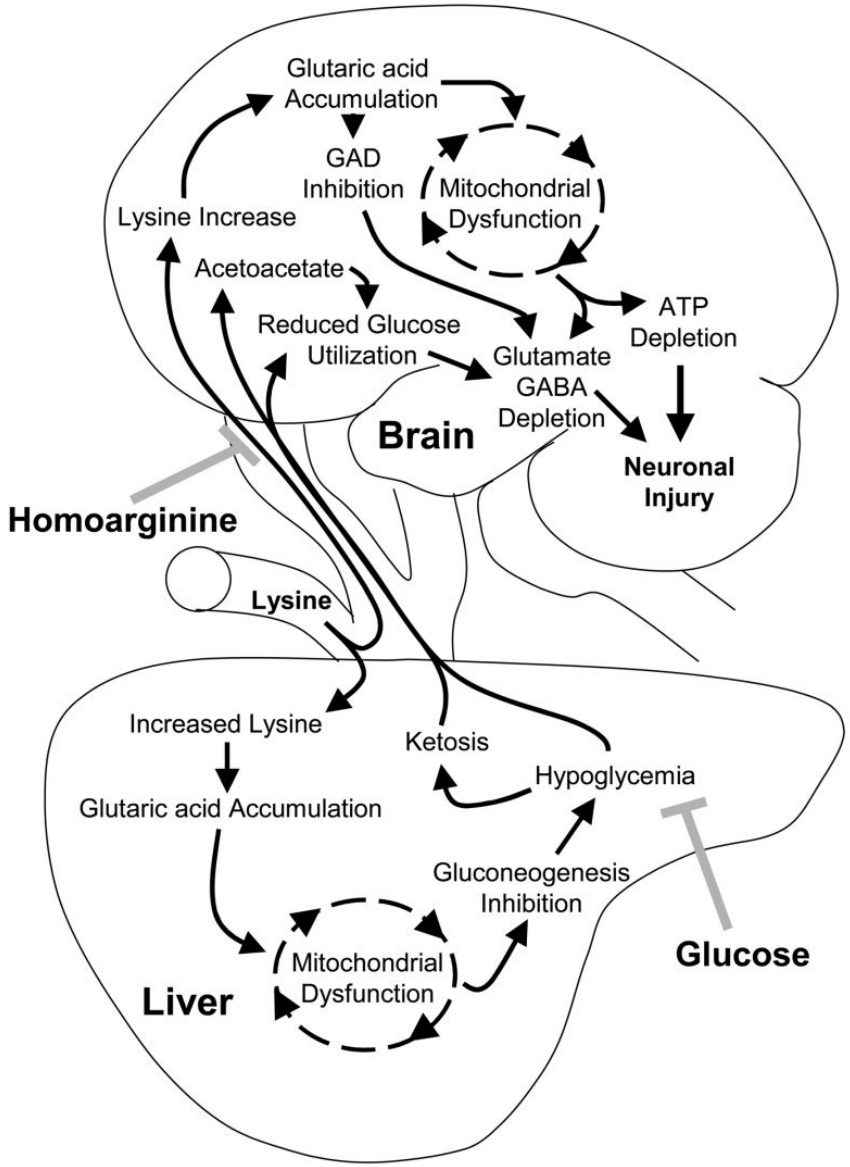
- Two biochemical subtypes depending on the amount of GA in urine
  - high (HE) and
  - low excretors (LE),

- New borns may develop normally
- Until 6 to 18 months
- Non specific catabolic stress results in

“acute encephalopathic crisis”

- **The brain at this stage is particularly dependent on ketones and ketogenic amino acids during periods of catabolic stress**

- In GAT1,
  - GA accumulates
  - Mitochondrial failure
  - Leads to neuronal death
  - Bilateral striatal injury



- **Macrocephaly and hypotonia**
- ***Irreversible neurologic symptoms***

Developmental regression
Movement abnormalities
Cognitive impairment
Coma

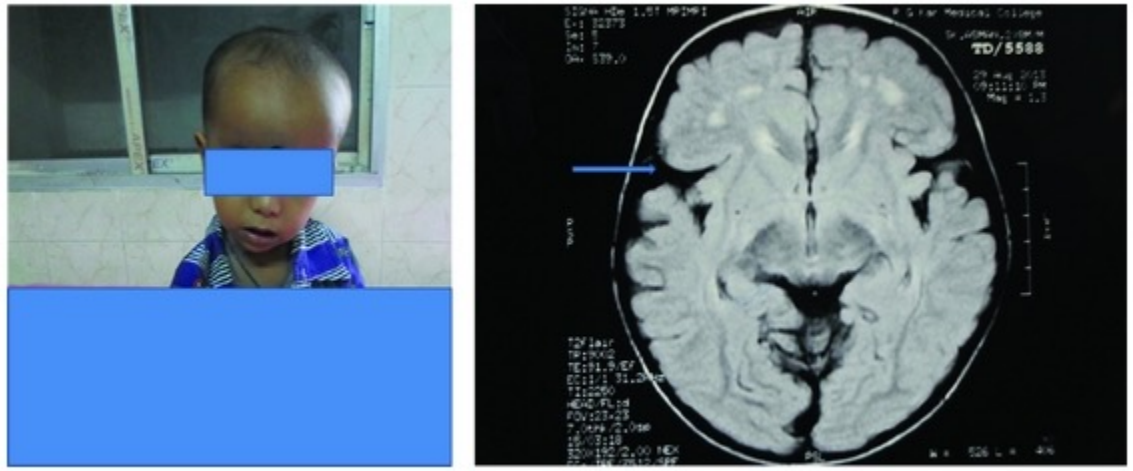


Figure 1. A case report from India
Macrocephaly, typical facies, and MRI of his brain reveals frontotemporal atrophy, dilated sylvian fissures with open opercula (arrow), diffuse hyperintense lesions in bilateral basal ganglia, and both frontal white matter and bilateral periventricular area. Widening of the sylvian fissure gives the characteristic “bat-wing” appearance.

Putsi et al (2014)

Misdiagnosis

- dystonic cerebral palsy
- battered child syndrome with chronic subdural effusions
- Encephalitis
- Reye’s syndrome
- familial infantile bilateral striatal necrosis
- familial megalocephaly
- sudden infant death syndrome
- and vaccine induced brain-injury.

- Increased levels of 3-OH-GA, typical in GA1 patients
  - short-chain 3-hydroxyacyl CoA dehydrogenase (SCAD) deficiency
  - patients with renal insufficiency,
  - in patients with disorders of long-chain fatty acid oxidation
  - mitochondrial disorders,
  - and in ketotic patients.

Diagnosis

- New born screening disease panels in many countries

- Abnormal newborn screening results is followed by quantitative analysis
- The diagnosis is confirmed by
  - significantly reduced enzyme activity
  - and/or detection of two disease-causing GCDH gene mutations

- using gas chromatography/mass spectrometry (GC/MS)
- electrospray-ionization tandem mass spectrometry (MS/MS).

- The characteristic metabolites in urine , plasma, CSF
  - GA
  - 3-OH-GA
  - glutaconic acid
  - glutarylcarnitine (C5DC)

- mutation analysis of the GCDH gene and/or GCDH enzyme analysis in leukocytes or fibroblasts.

Standard Therapies

- a low lysine diet
- supplementation of a lysine-free, tryptophane-reduced, amino acid mixture
- oral supplementation of L-carnitine
- an intensified emergency treatment during episodes of intercurrent illness or surgical interventions.

- INPATIENT MANAGEMENT

1) Treatment is URGENT even if the child seems to be in good overall condition. Avoid long waiting times.

2) Do not delay. Unless you are very confident and certain, treat with intravenous fluids.

3) If there is any doubt at all, the child must be admitted, even if only necessary for a short period of observation.

- Genetic counselling
- Family support

L-carnitine--metabolic functions and meaning in human's life
Pekala J, . Current drug metabolism, 2011 Sep;12(7):667-78.

- L-Carnitine is an endogenous molecule
- involved in fatty acid metabolism
- biosynthesized within the human body using amino acids: L-lysine and L-methionine, as substrates.
- found in many foods, beef and lamb, fish, poultry and milk.
- L-carnitine transports the chains of fatty acids into the mitochondrial matrix,
- allowing the cells to break down fat
- get energy from the stored fat reserves.
- L-carnitine and its esters help reduce oxidative stress
- studies have started to shed light on the beneficial effects of L-carnitine when used in various clinical therapies

nutrients

MDPI

Article

Inconsistencies in the Nutrition Management of Glutaric Aciduria Type 1: An International Survey

Laurie Bernstein [1,*], Curtis R. Coughlin [1], Morgan Drumm [1], Steven Yannicelli [2] and Fran Rohr [3]

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check for updates

- nutritional management approaches to identify current real-world experiences and how they compare to established guidelines.
- suggests that inconsistencies in practice exist in several major areas

- To most of the clinicians surveyed,

  diet liberalization and a “protein-controlled diet” means restricting intact protein intake to the standard reference

  - also means reducing the intake of medical food

  liberalization means no restriction of protein after 6 years of age.

Table 1
Clinical and laboratory findings in 14 known South African children with GA 1.

Patient	Age and sex at diagnosis	Presentation at diagnosis	Neuro-imaging	Urine GA (μmol/mmol creatinine)[a]	Urine 3-OHGA (μmol/mmol creatinine)[a]	GCDH activity in cultured fibroblasts (pmol.h^{-1} mg^{-1} protein)[a]	Ancestry	GCDH genotype	Phenotype
1	5 years, male	Dev. delay, dystonia	Typical	520[b]	113[b]	n.d.	African	A293T/A293T	Severe
2	12 months, female	Seizures, dev. delay	Typical	32.7	34.7	n.d.	African	A293T/A293T	Severe
3	3 days old, male	Asymptomatic macrocephaly, diagnosis by newborn screening	Typical	47.2	52.8	n.d.	African	A293T/A293T	Mild
4	8 months, male	Acute hypotonia with intercurrent illness, progression to dystonia	Typical	655	32.6	<10	African	A293T/A293T	Severe
5	4 years, male	Dev. delay, dystonia	Typical	[c]	[c]	n.d.	African	A293T/A293T	Severe
6	8 months, male	Acute hypotonia with intercurrent illness, progression to dystonia	Typical	300 270	37.3 59.6	50	African	A293T/A293T	Severe
7	16 months, male	Macrocephaly, focal seizures, dev. delay	Typical	17.2	10.4	<10	African	A293T/A293T	Severe
8	11 months, male	Dev. delay, dystonia	Typical	1149 562	84.8 54.4	50	African	A293T/A293T	Severe
9	27 months, female	Dev. delay, dystonia, macrocephaly	n.a.	30	9.5		African	n.d.	Severe
10	6 months, female	Progressive dev. delay and dystonia, after acute encephalopathic episode, macrocephaly	Typical	23.4	10.2	n.d.	African	A293T/A293T	Severe
11	6 months, male	Acute encephalopathy, seizures. Initial diagnosis of non-accidental injury.	Typical	10,000	48	n.d.	Mixed (African, European, East-Indian)	A293T/R402W	Severe
12	14 months, male	Progressive dev. delay	n.a	787	66	n.d	African	A293T/A293T	Severe
13	7 months, male	Dev. delay, hypotonia, dystonia	Typical	8548	79.6	<10	Asian	Q59P/Q59P[d]	Severe
14	16 months, female	Dev. delay, dystonia	Typical	625	96.3	n.d	African	A293T/A293T	Severe

-

Van Der Watt, G et al, 2010. Glutaric aciduria type 1 in South Africa – High incidence of glutaryl Co – A dehydrogenase deficiency in black South Africans. Molecular genetics and metabolism , 101, 178- 182.

CASE REPORT

A review of patients with glutaric aciduria type 1 at Inkosi Albert Luthuli Central Hospital, Durban, South Africa

R Govender,[1] FCPaed (SA); A Mitha,[2] FCRad (SA); L Mubaiwa,[1] FCPaed (SA)

- Retrospective review
- 6 patients, 2007 – 2015
- Mean age of diagnosis 12 months (2 - 22)
- 2 had premorbid delays
- First study in Africa to correlate their neuroimaging findings
- MRI findings – hyper intense basal ganglias,

widened perisylvian fissures,

abnormal signals in central peduncle and central tegmental tracts

- 1 gained milestones, 2 remained static , 3 neuroregression
- Only 2 patient adhered to the diet
- Rest declined due to cultural preferences

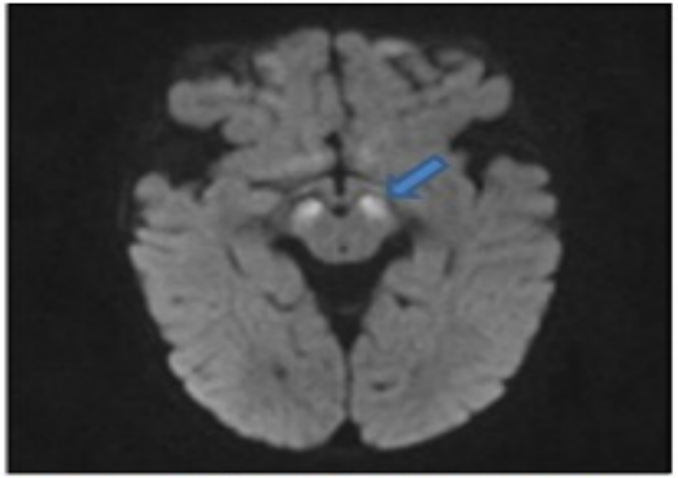


Fig. 2. A DWI (b=1 000) in the same patient as in Fig. 1, showing increased signal intensity in the cerebral peduncles and widened sylvian fissures.

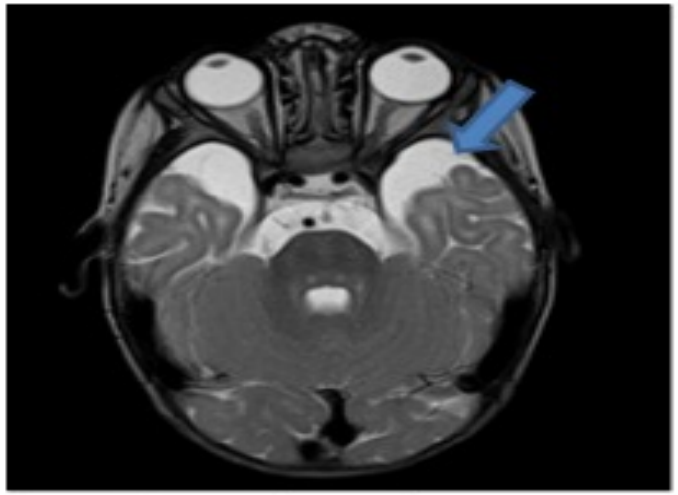
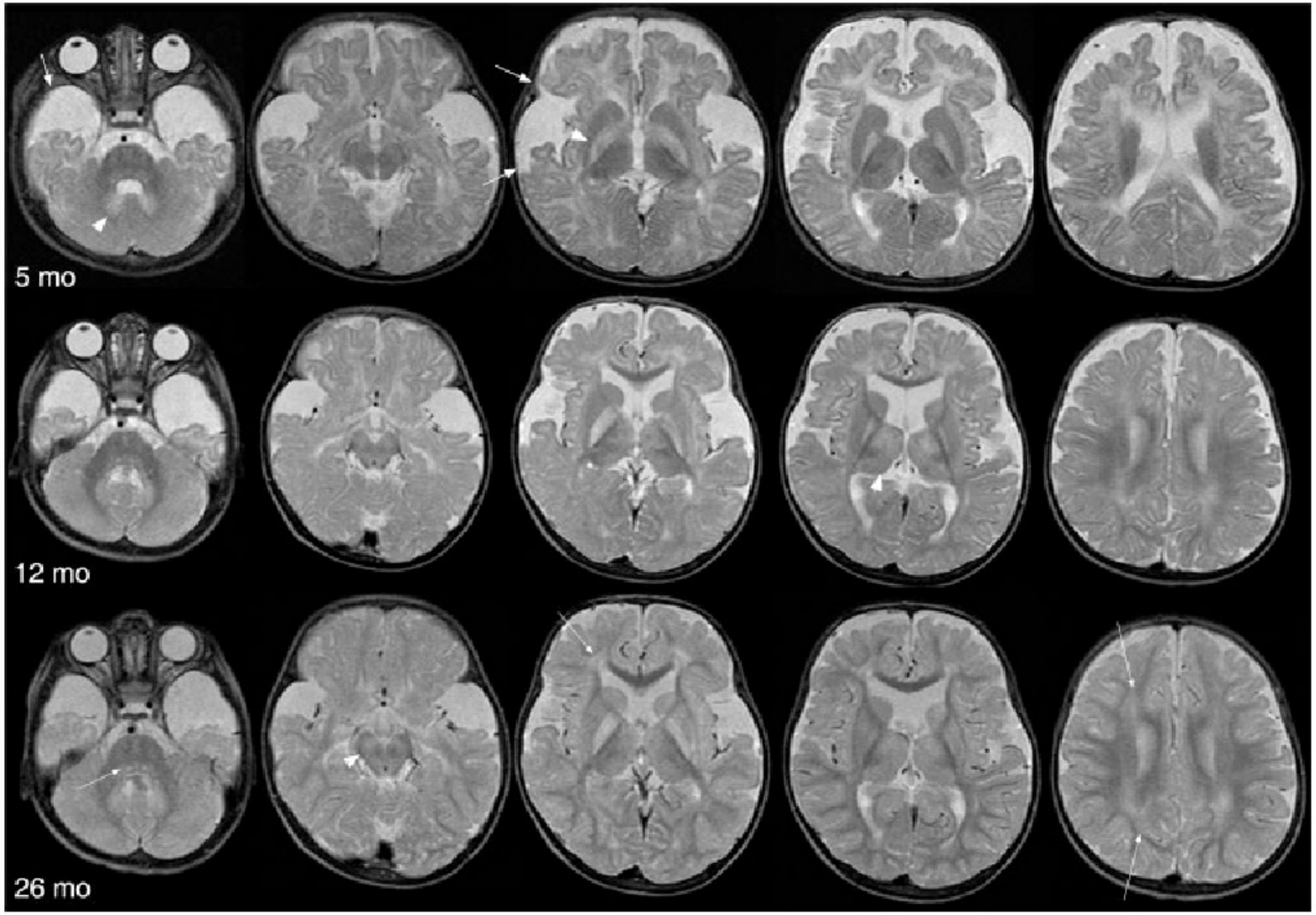


Fig. 3. A T2W axial MRI in the same patient as in Fig. 1, showing enlarged CSF spaces anterior to the temporal lobes and hyperintensity in the central tegmental tracts bilaterally.

Without early diagnosis and treatment

Striatal degeneration occurs in 80% of children before 2 years



Sequential MRIs in a child diagnosed in the first weeks of life :

- frontotemporal hypoplasia: widening of anterior temporal and sylvian CSF spaces
- Deep grey matter involvement is atypical with T2 hyperintensity initially of pallidum and dentate nucleus, subsequently also of thalamus and of the substantia nigra
- With time the striatal signal increases
- 26 months - incomplete myelination of the anterior temporal and fronto basal subcortical white matter
- symmetrical T2 hyperintensity of the periventricular and lobar white matter and of the central tegmental tracts becomes more prominent

Harting et al. 2009

For 80-90% of people with GA T1
motor symptom development is preventable,
requires early diagnosis by newborn screening and treatment from birth.

New born screening

- aimed at improving the neurologic outcome and untimely death of symptomatic individuals.
- Late 1990s, first NBS pilot studies
- Australia, Germany, some US Federal States
- genetic high-risk populations (Amish Community, Pennsylvania, USA; Oji-Cree First Nation, Canada; and Irish Travellers, Republic of Ireland).
- More than 20 years later
- This meta-analysis
  - superior neurologic outcome with a higher rate of normal motor development
  - a lower rate of acute or insidious onset of MD compared with patients identified by TMS.
- Accordingly, it is a significant progress that a growing number of countries worldwide (e.g., 17/29 European Union member states, according to the International Society for Neonatal Screening) have meanwhile included GA1 in their national NBS programs or NBS pilot studies

and this guide the decision of governments of those countries who have not so far.

- Systematic review, 2000 to 2019 on outcomes of NBS
- 15 publications
- In the NBS group (*n* = 261 patients),
  - 74. 7% patients remained asymptomatic
  - 25.3% developed a Movement Disorder.

- 20% received a non recommended diet (diet details not reported)
- 66.6% recommended Emergency treatment (Info not included)

Children developed neurologic symptoms

- deviated from the recommendations

Impact of newborn screening and quality of therapy on the neurological outcome in glutaric aciduria type 1: a meta-analysis
Boy N. et al
Genetics in Medicine volume 23, pages13–21 (2021)

Quality of Treatment in children screened at birth

full adherence to recommendations for both MT and ET was associated with the best neurological outcome and the highest rate of asymptomatic patients (93%)

while 50% of patients with non recommended MT and 100% of patients with non recommended ET developed a complex MD.

deviations from MT increases the risk of insidious onset MD

deviations from ET being highly frequent in individuals with acute onset MD.

major predictor of neurological outcome in a screened population of GA1.

JIMD Reports
DOI 10.1007/8904_2014_360

RESEARCH REPORT

Neurodevelopmental Profiles of Children with Glutaric Aciduria Type I Diagnosed by Newborn Screening: A Follow-Up Case Series

Amy Brown · Louise Crowe · Miriam H. Beauchamp · Vicki Anderson · Avihu Boneh

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- neurological damage can occur in the absence of an encephalopathic crisis due to neurotoxicity in utero or early life and that this may be associated with delayed myelination and brain maturation
- supported by findings of brain abnormalities and widening of the sylvian fissures and fronto-temporal atrophy in newborns and as early as 33 weeks gestation which may resolve over time.
- NBS generally have average intelligence, although they may be vulnerable to more subtle deficits in language and speech and fine motor skills.
- Environmental factors can act as protectors or increase vulnerability.
- This has been referred to as the ‘double hazard theory’
- environmental factors such as socioeconomic background, family functioning and social support are largely unmentioned

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RESEARCH REPORT

Neurodevelopmental Profiles of Children with Glutaric Aciduria Type I Diagnosed by Newborn Screening: A Follow-Up Case Series

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- 6 patients , neuropsychological testing at 3 years and 6 years
- Fine motor skills were below average in all patients.
- Speech improved following speech therapy.
- IQ scores remained generally stable within the normal range.
- Executive functioning was average to high average in four patients.
- Behaviour, as assessed through parental questionnaires, was problematic in two patients
- Compounding factors included child neglect, family history of autism and multiple admissions to hospital (n ¼ 1 in each).

- GA-I affects fine motor skills and speech, regardless of early treatment, but not IQ scores.
- Patients with GA-I should be referred for assessment and appropriate early intervention.
- Further research is
  - correlate specific neuropsychological deficits with neuroimaging
  - is their brain vulnerability after age 5 years.

Molecular Genetics and Metabolism 131 (2020) 325–340

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Glutaric acidemia type 1: Treatment and outcome of 168 patients over three decades

Kevin A. Strauss[a,b,c,*], Katie B. Williams[a], Vincent J. Carson[a,b], Laura Poskitt[a,b], Lauren E. Bowser[a], Millie Young[a], Donna L. Robinson[a], Christine Hendrickson[a], Keturah Beiler[a], Cora M. Taylor[d], Barbara Haas-Givler[d], Jennifer Hailey[e], Stephanie Chopko[f], Erik G. Puffenberger[a], Karlla W. Brigatti[a], Freeman Miller[g], D. Holmes Morton[a,b,h]

- No neurologic injuries occurred after 19 months of age.

- Adherence to metabolic formula and L-carnitine supplementation declined by age 7 years.

- altered plasma amino acid and carnitine concentrations
- but resulted in no serious adverse outcomes.
- The need for dietary interventions and emergency IV therapies beyond early childhood is uncertain.

Piercy et al. BMC Pediatrics (2019) 19:349
https://doi.org/10.1186/s12887-019-1742-x

BMC Pediatrics

RESEARCH ARTICLE Open Access

What are the information needs of parents caring for a child with Glutaric aciduria type 1?

Hilary Piercy[1*], Mildrid Yeo[2], Sufin Yap[3] and Anthony R. Hart[3]

- A focus group with five parents was conducted to gain insights

- 'Understanding the condition'
  and to be aware of the worst-case scenario
- 'Managing the condition'
  how parents co-ordinated and controlled the involvement of other carers

- the importance of addressing parents' initial and ongoing informational needs so they can fulfil their role and protect their child from metabolic harm.

- The complexity of the scientific information makes this particularly challenging

- highlighting the importance of co-production approaches for any initiatives to develop materials or ways of working

DECOMPENSATION TRIGGERS (factors that cause protein breakdown)

1. Fasting
2. Insufficient intake
3. Typical childhood illnesses, particularly , particularly **VOMITING and DIARRHEA, WITH OR WITHOUT FEVER**
4. Fever (from any cause)
5. Intense physical exercise
6. High protein intake (dietary transgression)

TREATMENT

- REGULAR OR SLIGHTLY HIGH CALORIE LOW LYSINE/TRIPTOFAN DIET
- LOW TRIPTOFAN/LYSINE FREE AMINOACID SUPPLEMENTS
- CARNITINE SUPPLEMENT
- PREVENT ACUTE DECOMPENSATION

HOW TO PREVENT ACUTE DECOMPENSATION:

- ✓ AVOID HIGH PROTEIN INTAKE
- ✓ AVOID PROLONGED FASTING (5 hours in maintenance treatment, 2 hours in case of intercurrent febrile infection and risk situations).
- ✓ If at risk of acute decompensation, start outpatient **EMERGENCY TREATMENT** at the slightest suspicion and without delay.

FamiliasGA, Emergency protocol

‘A country cannot declare health equity for all, until it caters for the needs of rare conditions’

- IEM are rare
- Extremely important to determine since
  - specific therapies may be available
  - Acute metabolic decompensation may be avoidable
- In Africa newborn screening may not be available to the population
- Clinical acumen and prompt referral becomes the driver for investigations at centres where resources are accessible at the hands of expert teams

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FamiliasGA, Emergency protocol

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