
بسم الله الرحمن الرحيم

GALACTOSEMIA

Soroor Inaloo

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Pediatric Neurologist

HISTORY

- The first description of a neonate with galactosemia was in 1908
- In 1935, the case of an infant with hypergalactosemia and galactosuria who responded well to a lactose-restricted diet at 10 months of age was described
- In 1956, GALT enzyme was identified
- In 1988 the *GALT* gene was identified

INTRODUCTION

- Classical galactosemia is an autosomal recessive Mutations of the GALT gene
- Reduced function of the enzyme galactose-1-phosphate uridyltransferase (GALT) and subsequent accumulation of galactose-1-phosphate (Gal-1-P), galactose, and derived metabolites
- Estimated prevalence of 1:30,000 newborns Diagnosis can be established by demonstrating increased levels of erythrocyte Gal-1-P and decreased activity of erythrocyte GALT (<5%)

- Despite adequate treatment, surviving patients may develop long-term complications, such as premature ovarian failure and central nervous system (CNS) dysfunction, including cognitive difficulties, psychiatric symptoms, and speech and motor problems
- To date, motor complications have been reported in 18%–45% of patients, with the most common features being tremor and cerebellar ataxia
- There is still debate about whether galactosemia is a progressive neurodegenerative disorder or whether symptoms result from damage sustained in the prenatal period.

- Accumulation of galactose and derived toxic metabolites, such as Gal-1-P or galactitol, has long been thought to be the main cause of cellular damage in galactosemia
- It has been suggested that, despite strict dietary galactose restriction, endogenous production of galactose could cause continuous intoxication
- One study found a correlation between the presence of verbal dyspraxia and mean levels of Gal-1-P, as well as with total galactose oxidation

- 47 patients
- 31 patients showed evidence of motor dysfunction including: tremor (23 patients), dystonia (23 patients), cerebellar signs (6 patients), and pyramidal signs (4 patients) Mirror movements were present in 14 of 47
- Tremor and dystonia were often combined (16 patients)
- Thirteen patients reported motor symptoms, with 8 describing progressive worsening
- **Nonmotor neurological features** (cognitive, psychiatric, and speech disorders) and premature ovarian failure were more frequent in patients with motor dysfunction
- **Motor dysfunction is a common complication** of classical galactosemia, with tremor and dystonia the most frequent findings
- Up to one third of patients report motor symptoms and may benefit from appropriate treatment
- Progressive worsening is not uncommon
- Movement Disorders, Vol. 28, No. 6, 2013

Reference	Patients included (region)	Patients available for motor assessment	Population studied (% of adults)	Method	Frequency of motor dysfunction (%)
Waggoner et al, 1990[2]	350 (US and Europe)	206	Children and adults (17)	Questionnaire	37/206 (18)
Scweitzer et al, 1993[3]	134 (Germany)	78	Children	Direct Examination	29/78 (37)
Kaufman et al, 1995[4]	45 (US)	45	Children and adults (?%)	Direct examination	12/45 (26)
Hughes et al, 2009[5]	28 (Ireland)	28	Children and adults (?%)	Direct examination	7/28 (23)
Waisbren et al, 2012[7]	33 (US)	33	Adults (100%)	Direct examination	15/33 (45)
Present report	47 (UK)	47	Adults (100%)	Direct examination	31/47 (66)

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MOTOR FEATURES

- Dystonia : (49 %)focal ,segmental , generalized
- Tremor : (49 %)action ,postural ,resting ,bilateral ,arm ,head
- Mirror movement : (30 %)
- Cerebellar dysfunction : (13 %) ataxic gait, limb dysmetria, cerebellar dysarthria
- Pyramidal signs : (9%) brisk reflexes and ankle clonus , extensor plantar responses, spastic paraparesis, pseudobulbar syndrome
- Eye movement abnormalities : (9%) broken pursuit , square-wave jerks , oculomotor apraxia , strabismus

TABLE 3. Motor phenotype of symptomatic and asymptomatic patients

	Symptomatic (n=13)	Asymptomatic (n=18)
Tremor, n (%)	11 (85)	12 (67)
Head	4 (31)	0
Upper limbs	11 (85)	12 (67)
Asymmetric	6 (46)	2 (11)
Rest	2 (15)	0
Postural	9 (69)	10 (56)
Kinetic	8 (62)	4 (22)
Lower limbs	1 (8)	0
Dystonia, n (%)	10 (77)	13 (72)
Distribution		
Generalized	4 (31)	0
Segmental	6 (46)	4 (22)
Focal	0	5 (28)
Multifocal	0	4 (22)
Region involved		
Face	4 (31)	2 (11)
Jaw	2 (15)	0
Neck	10 (77)	3 (17)
Arms	9 (69)	12 (67)
Trunk	4 (31)	0
Legs	3 (23)	4 (22)
Dystonia and tremor, n (%)	9 (70)	7 (39)
Mirror movements, n (%)	6 (46)	8 (44)
Cerebellar signs, n (%)	5 (39)	1 (6)
Pyramidal signs, n (%)	3 (23)	1 (6)
Eye-movement abnormalities, n (%)	4 (31)	0

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NON MOTOR FEATURES

- Nonmotor neurologic features is common (55%)
- Cognitive problems: (32 %) learning difficulties, performance and/or verbal IQ80
- Neuropsychiatric symptoms : (23 %)including anxiety , depression , suicide attempt, obsessive-compulsive disorder , autistic spectrum disorder , social phobia , and paranoid delusions
- Speech problems : (34%) including delay in speech development and speech apraxia

BRAIN IMAGING

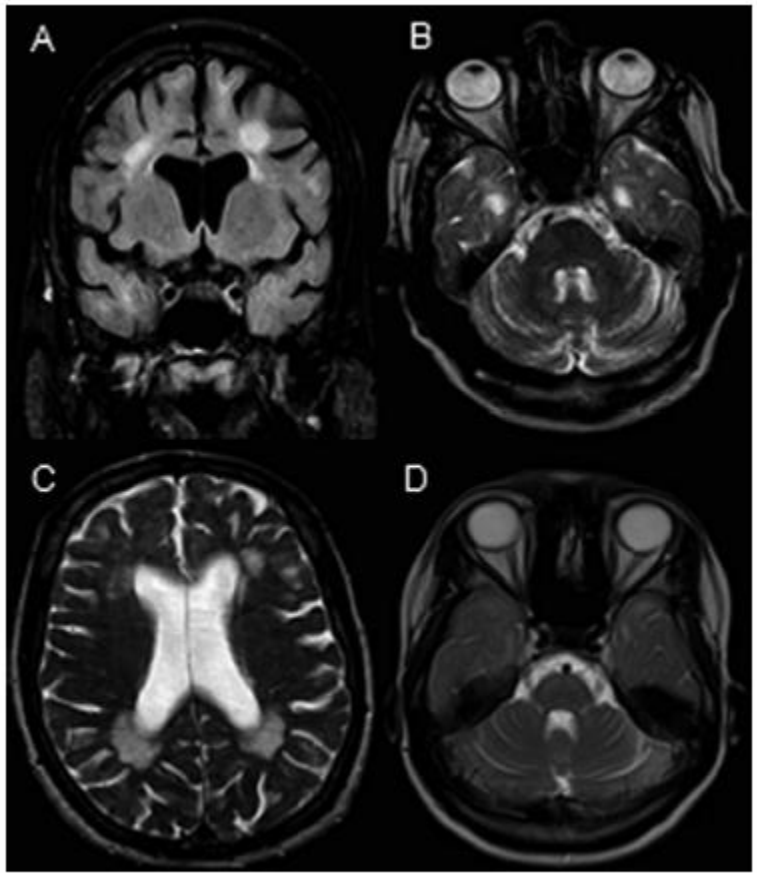

FIG. 2. Imaging findings. Coronal FLAIR (**A**), axial T2-weighted images (**B, C, D**) belonging to 2 patients. **A–C:** First patient. Note moderate cerebral subcortical and cerebellar atrophy; symmetrical, confluent periventricular, and subcortical hyperintense signal changes in cerebral white matter. **D:** Second patient. Note modest pontine and cerebellar atrophy.

MECHANISMS OF CNS INVOLVEMENT

- Accumulation of galactose and derived toxic metabolites, such as Gal-1-P or galactitol, has long been thought to be the main cause of cellular damage in galactosemia
- Another possible cause for cellular damage is a secondary deficiency Galactosemia is associated with UDP-galactose deficiency, which does not revert completely with diet, simulating congenital defects of glycosylation
- Abnormal lipid and protein glycosylation may be relevant for myelin synthesis and may also interfere with intracellular signaling pathways, resulting in pleiotropic effects, among them altered gene expression
- Inositol deficiency, secondary to accumulation of galactitol and Gal-1-P, has also been shown in patients with galactosemia
- This cellular osmolyte is also the precursor of inositol-phosphatides, which are crucial for intracellular signaling and vesicle trafficking
- Its deficiency, particularly in the prenatal period, could result in central nervous system damage

- Patients with evidence of motor dysfunction also had a higher frequency of other nonmotor neurological features, including cognitive impairment, psychiatric problems, and speech difficulties, suggesting a common pathogenic mechanism leading to widespread CNS damage
- Premature ovarian failure was also more common in the group with motor dysfunction
- The underlying biochemical mechanisms leading to CNS damage remain uncertain
- Genetic factors are likely to play a role; for example, patients homozygous for the Q188R mutation have been shown to have a more severe phenotype

RISK FACTORS

- Neurological complications were less prevalent in subjects with age below 18 years
- In patients diagnosed following NBS
- Started on diet therapy in the first week of life
- Patients with a strict diet (lactose restricted and restrictions in fruit and vegetables) developed neurological complications more frequently than patients with a less strict diet
- An enzyme activity ≤ 1%
- Homozygosity for p.Gln188Arg

- Moderate liberalization of galactose intake (suggested due to galactose's importance for glycosylation of glycoproteins and glycolipids) has been shown to improve IgG glycosylation in a small subset of pediatric and adult patients
- It is possible like other inborn errors of metabolism requiring substrate precursors that a minimum amount of exogenous dietary galactose is necessary for all CG patients. Our results support the moderate liberalization of diet that is recommended nowaday

A total of 509 patients (48.1% male and 51.9% female) from 15 countries were included; data was collected from December 2014 to July 2018

Rubio-Gozalbo et al. Orphanet Journal of Rare Diseases (2019) 14:86

The natural history of classic galactosemia: lessons from the GalNet registry

	n	Valid n	%
Developmental delay infancy/childhood	167	320	52.2
Motor	18		10.8
Cognitive	66		39.5
Motor and cognitive	83		49.7
Language delay[b]	128	164	78.0
Isolated language delay	37	170	21.8
Language and speech disorders[a]	192	289	66.4
Speech defect	129	315	41.0
Impairment in vocabulary	117	288	40.6
Impairment in grammar	98	253	38.7
Verbal dyspraxia	67	285	23.5
Dysarthria	49	246	19.9

Neurological complications[a]	168	323	52.0
Tremor	104	336	31.0
General motor abnormality	86	319	27.0
Ataxia	40	329	12.2
Seizures	26	320	8.1
Dystonia	24	318	7.5

Mental (psychiatric) and behavioral problems[a]	128	288	44.4
Anxiety disorder	67	300	22.3
Depression	38	303	12.5
ADHD	21	286	7.3
Autism spectrum disorder	17	281	6.0

THANK YOU FOR YOUR ATTENTION