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Short Communication

# Natural history of three late-diagnosed classic Galactosemia patients

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ABSTRACT

The authors report the natural history of three patients with late-diagnosed Classic Galactosemia (CG) (at 16, 19 and 28 years). This was due to a combination of factors: absence of neonatal screening, absence of some typical acute neonatal symptoms, and negative galactosemia screening. This report underlines the value of neonatal screening and the importance of further diagnostic testing in case of late-onset manifestations.

## 1. Introduction

Classic galactosemia (CG, OMIM: galactosemia I, #230400) is an autosomal recessive disorder characterized by deficient galactose-1-phosphate:uridylyltransferase activity (GALT; EC 2.7.7.12) due to biallelic pathogenic *GALT* variants http://www.arup.utah.edu/database/GALT/GALT_display.php. Untreated, it can result in neonatal life-threatening complications, including feeding problems, failure to thrive, hepatocellular damage, bleeding, and *E coli* sepsis [1,2]. A galactose-restricted diet, reported for the first time in 1935, resolves the neonatal clinical picture, but later on most patients develop complications affecting mainly the central nervous system and the female gonads [3–8]. This results in cognitive, neurological and behavioral disability, primary ovarian insufficiency (POI), and subsequent subfertility in female patients [9,10]. The underlying pathophysiologic mechanism of these long-term complications is poorly understood [11].

Patients with untreated CG may show a type 1 or a type 2 serum transferrin isoelectrofocusing (IEF) pattern. Hence CG is considered a secondary Congenital Disorder of Glycosylation (CDG) [12–16]. NBS for CG, which can help to reach a timely diagnosis, is not universally implemented. We report the natural history of three patients with late-diagnosed CG.

## 2. Patient reports

*Patient 1* was born after an uneventful 41 weeks of pregnancy and a caesarian section as the first and only child of second-degree-related parents. Weight at birth was 2450 g, length 47 cm and head circumference 32 cm. Apgar score was 5 /10. She was breastfed. At one month, she was admitted because of prolonged feeding difficulties, failure to thrive, vomiting, diarrhea and recurrent infections. Clinical examination showed strabismus, nystagmus and hypotonia. Biochemical screening

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showed normal serum electrolytes, creatinine, transaminases and albumin, normal urinary organic acids and plasma amino acids, and slightly decreased free and total serum carnitine. Head control was achieved at four months and sitting with support at 13 months. At six months, she developed complex partial seizures characterized by episodes of ocular retroversion. She started to walk at 15 months. At two years and five months, there were epileptic crises with complex partial seizures like "absences", with a frequency of about once a month. Electroencephalogram (EEG) showed focal paroxysmal epileptic activity. Brain magnetic resonance imaging (MRI) showed extensive bilateral white matter lesions involving both cerebral hemispheres, brainstem and cerebellum as well as leukodystrophy with diffuse demyelination with extension to the upper cervical cord, cerebellar hypoplasia and subcortical atrophy.

At six years and ten months she suffered from severe intellectual disability and kyphoscoliosis. Brain auditory evoked potentials were normal.

During childhood, height and weight followed the 5th percentile. Her scoliosis was surgically corrected at the age of 12 years. She reached puberty spontaneously with menarche at 12 years of age. Her clinical picture stabilized during adolescence and early adulthood.

At 28 years old, she weighs 38 kg and has severe cognitive impairment with absence of speech, but smiles, makes contact with gaze, and calls using moan sounds. She presents generalized hypotonia, tetraparesis and paresis of face and neck muscles, without spasticity nor dystonia. Lower members' ligament retraction and pain on mobilization of the right leg suggests hip dislocation. Menstruations are still regular. The epilepsy is under control with carbamazepine 3 times 100 mg/day. Serum follicle-stimulating hormone, luteinizing hormone, anti-müllerian hormone and 17-estradiol were evaluated for the first time at the current age and are normal.

Liver tests, including serum transaminases and bilirubin, remained normal (up to her actual age of 28 years). Serum transferrin IEF showed a type 1 pattern.

The type 1 transferrin IEF pattern was further investigated. Phosphomannomutase activity and lipid-linked oligosaccharide incorporation in fibroblasts were normal. The final diagnosis was obtained through massive parallel sequencing (target capture CDGv1, Nimblegen). Sequence validation of whole exome sequencing (WES, open exome) data and segregation analysis were performed by Sanger sequencing of PCR products amplified from genomic DNA of the GALT gene. The patient is compound heterozygous for the reported pathogenic variant c.563 A > G (p.Gln188Arg), and a novel variant c.794C > G (p.Pro265Arg). The nomenclature of the variants is based on transcript NM_000155.3. This novel variant is not listed in gnomAD [17]. The CADD of the novel variant is well above the cut-off of deleteriousness, with a score of 20.8, and Varsome classification is likely pathogenic. Furthermore, an alternative variant, p.Pro265Ala, has already been classified as pathogenic [18,19]. The deleteriousness of this combination of variants was confirmed by the observation of undetectable erythrocyte GALT activity, increased erythrocyte galactose-1-phosphate (Gal—1P, 390 μmol/L; normal range: 7–22), and increased urinary galactitol (226 mmol/mol creatinine; normal range: 2–9).

*Patient 2* was the second child of non-consanguineous parents. At 18 days, he was hospitalized for severe failure to thrive, vomiting and jaundice. He had hepatomegaly (5 cm), increased serum transaminases and cholestasis. Galactose was absent in urine. We unfortunately do not know whether he was on i.v. glucose at the time of urine sampling. There was generalized aminoaciduria. A liver biopsy showed cholestasis with bile thrombi, irregular arrangement of parenchymal cells, vacuolization, regenerative abnormalities and liver fibrosis. Neonatal hepatitis was suspected, but serology for several viruses was negative. A liver biopsy was repeated at four months and showed increased portal and parenchymatous fibrosis and cirrhosis. Feeding tolerance (type of formula unknown) improved, and he was discharged at 4.5 months. He showed global developmental delay (language/speech and motor) and developed aggressive and maladjusted behaviour. At two years old, he was hospitalized for additional testing. Blood/serum cholesterol, lipids, ammonia, glucose, copper, ceruloplasmin, urinary organic acids, glycosaminoglycans, and serology were normal. The ophthalmological examination was normal. Cholestasis and liver enzymes improved gradually and normalized after eight years. Repeated liver biopsies showed improvement in fibrosis and later stable cirrhosis.

At four years old, he could walk but on his toes. EEG showed irritative abnormalities in both hemispheres. Computed tomography (CT) of the brain and chromosomal analysis were normal.

At seven years, height and head circumference were on the 10th centile and weight on the 30th centile. Problems with walking, speech and behaviour persisted, and he lived in a healthcare institution. His developmental delay was estimated to be two years. He suffered from frequent seizures under antiepileptic therapy. At 15 years he had spasticity, needed adapted shoes and had botox injections. At 16 years old, he fractured the right tibia and fibula.

At 16 years, a geneticist visited his healthcare institution, and diagnostic testing was performed. A broad genetic metabolic screening revealed a type 1 serum transferrin IEF. Urinary galactitol (356 μmol/mmol creatinine, normal <6) and galactose (421 μmol/mmol creatinine, normal <22) as well as erythrocyte Gal-1P (2.6 μmol/g Hb, normal <0.58) were all increased. Erythrocyte GALT activity was 0.2 μmol/h/g Hb (normal 32.8 ± 5.4). Genetic analysis revealed two known *GALT* variants: c.563 A > G (p.Gln188Arg) and c.756G > T (p.Gln252His). A galactose-restricted diet was initiated at 18 years. Gal-1P level and the transferrin pattern normalized and the galactitol level decreased but did not normalize as expected in CG (Table 1). At the time of diagnosis, he already suffered from spasticity, particularly in the lower extremities, pes equines, epilepsy, severe myopia and cataract. A bone densitometry at 19 years revealed a bone mineral density (BMD) of the spinal column of Z = -1.6 (in adult CG, mean BMD of the spinal column is −0.94 [20–22]. At 40 years, he is still unable to talk and uses a walking device.

*Patient 3* was the first child of unrelated parents. As a newborn, she refused feeding and had gastroesophageal reflux. At six weeks, she had hypovolemic shock. Clinical examination revealed a distended belly without hepatosplenomegaly. She was treated with intravenous fluids, glucose and required erythrocyte infusions. She had a transient increase of serum transaminases. Blood ammonia, serum Gal-1P (after transfusion) and excretion of glycosaminoglycans and oligosaccharides were normal. The serum C24/C22 ratio was increased, and urinary organic acid analysis showed lactic aciduria and signs of liver dysfunction. Serum transferrin IEF showed a type 2 pattern. Two days after hospitalization, pronounced ascites developed, which normalized with diuretics. After stabilization, the patient received a low-protein diet and a hydrolyzed formula (without galactose), which was well tolerated. Vitamin D, vitamin E and anti-reflux medication were introduced. The patient was discharged after 2 weeks. Weight improved, and one month after discharge growth continued on the 10th percentile and there was no vomiting. Repeat serum transferrin IEF (with hydrolyzed formula not containing galactose) and phosphomannose isomerase and phosphomannomutase activities in leukocytes were normal. Congenital fructose intolerance and metachromatic leukodystrophy were ruled out. The phenotype partly resembled galactosemia but a classic GALT defect seemed unlikely with a repeatedly normal Gal-1P on dried blood spot.

In the following year, she needed tube feeding and developed an aversion to solid foods. The parents had noticed improvement with a lactose-restricted diet from a very early age. The patient refused butter and preferred very ripe cheeses.

Development had been normal with unsupported sitting at 6 months and walking and talking at 14 months, but a developmental delay became apparent at 2 years. Brain MRI showed signs of leukodystrophy with temporal lobe hyperintense zones, which remained stable.

At four years old, she could ride a regular bike. At six years, IQ testing revealed a global score of 62. She could swim at seven years. She went to a special education program, but due to unhappiness, went to regular

**Table 1**
Laboratory results in the three patients.

| | Patient 1 | | Patient 2 | | Patient 3 | |
|---|---|---|---|---|---|---|
| | Before treatment | During treatment | Before treatment | During treatment | Before treatment* | During treatment |
| GALT activity (μmol/h/g Hb) | 0 | | 0.2 ($N = 32.8 \pm 5.4$) | | 0 | 1 ($N = 18$–25) |
| Gal-1P | 390 μmol/L ($N < 22$, in erythrocytes) | | 2.6 μmol/g Hb ($N < 0.58$, in erythrocytes) | 0.33/ 0.8 μmol/g Hb ($N < 0.58$, in erythrocytes) | ?/ 520 μmol/L ($N < 600$, in DBS) | 295/ 620/ 528 μmol/L ($N < 600$, in DBS) |
| Galactitol in urine (μmol/mmol creatinine) | 226.1 ($N < 6$) | | 356 ($N < 6$) | 86 ($N < 6$) | 142 ($N < 14$) | 72, 114, 151 ($N < 14$) |
| Galactose in urine (μmol/L) | | | 421, 912 ($N < 22$) | 4–6 ($N < 22$) | | |
| Transferrin IEF pattern | Type 1 | | Type 1 | Normal | Type 2, normal, type 2, normal | |
| Genetic variants | c.563 A > G (p.Gln188Arg), c.794C > G (p.Pro265Arg) | | c.563 A > G (p.Gln188Arg), c.756G > T (p.Gln252His) | | c.563 A > G (p.Gln188Arg), c.563 A > G (p.Gln188Arg) | |

Abbreviations:?: unknown value; μmol/h/g Hb: μmol/h/g hemoglobin; DBS: dried blood spot; Gal-1P: galactose-1-phosphate; GALT: galactose-1P-uridyltransferase; IEF: isoelectrofocusing; N: reference values.

* Parents had already started lactose-restricted diet at a very early age based on complaints after lactose intake.

education with support.

At 12 years, she had delayed puberty and growth stagnation. She had signs of hypergonadotropic hypogonadism, (increased LH 6.8 U/L (normal range: follicular 2–13, periovulatory 14–96, luteal 1–11, postmenopausal 8–59) and FSH 22 U/L (normal range: follicular 3–13, ovulatory 5–22, luteal 2–8, postmenopausal >26), decreased estradiol 38.9 ng/L (normal range: follicular 12–166, periovulatory 86–498, luteal 44–211, menopausal <55) and severely impaired ovarian reserve with anti-müllerian hormone <0.42 μg/L (normal range 0.66–8.42). Genetic testing for Turner syndrome was negative. Estrogens were started to induce puberty. Bone densitometry revealed a spinal column BMD T score = −4.5 (mean spinal column BMD is $T = -1.1$ in adult CG [9]. At age 15, she was diagnosed with Crohn disease treated with several medicines and a hemicolectomy.

Additional testing again showed a type 2 serum transferrin IEF pattern, but a repeat test was normal.

At 19 years old, she had developed dyscalculia, dyspraxia and dyslexia. Clinical examination showed a small skull and a gothic palate, a slow reaction rate and discrete positional tremor. Brain MRI showed unchanged leukodystrophy. MRI spectroscopy showed normal choline/creatine and choline/*N*-acetylaspartate ratio. WES showed the known *GALT* variant, c.563 A > G (p.Gln188Arg) in homozygosity. Repeat DBS Gal-1P was 520 μmol/L (normal range <600), urinary galactitol 142 mmol/mol creatinine (normal range 0–14) and erythrocyte GALT activity was undetectable. The diet, which was already largely lactose-restricted, was intensified. Imuran (contains galactose) was discontinued under careful gastrointestinal observation. Bone densitometry showed some improvement (BMD $T = -2.5$), probably as a result of estrogen administration. At 24 years, the patient suffers from a therapy-resistant tremor. She works as a packager at a sheltered workplace.

## 3. Discussion

We describe the natural history of three CG patients from Portugal, Belgium and The Netherlands, with a late diagnosis of CG. The patients were diagnosed only in adulthood due to a combination of factors.

Firstly, the absence of neonatal screening for CG. In Portugal and Belgium, neonatal screening for CG has not been implemented yet. In The Netherlands, it was implemented in 2007, after the birthdate of this Dutch patient.

Secondly, the absence of some acute neonatal symptoms such as increased serum transaminases, bleeding diathesis, encephalopathy or hypoglycemia that are generally considered to be typical for CG, as in patient 1. A natural history study by the GalNet in 2019, described neonatal symptoms in CG patients. Of patients with CG, 70% had elevated transaminases, 43% bleeding diathesis, 29% encephalopathy, 25% hypoglycemia and 27% signs of infection. Eighty percent of patients presented with one or more of these acute clinical manifestations [9]. However, up to 1 in 5 CG patients present with non-acute clinical manifestations including the absence of increased serum transaminases. These results suggest that CG should be considered in any patient with severe failure to thrive and vomiting, in particular but not limited to patients in which there are neurological manifestations. At a later age, symptoms may be more non-specific and CG may not be considered. Other suggestive symptoms at a later age may include unexplained developmental delay (present in 52% of CG patients), neurological symptoms (52%), especially tremor (31%), motor abnormalities (27%), and psychiatric or behavioral disorders (44%). In women, late or induced puberty (49%) and POI (80%) are suggestive symptoms [9]. The refusal of galactose/lactose-containing products or a presumed cow's milk allergy may also be diagnostic clues.

Thirdly, a negative galactosemia screening may detract from the diagnosis. Gal-1P was normal in patient 3, first after erythrocyte transfusion and later after a galactose-restricted diet due to the suspicion of cow's milk allergy. We also observed that some of the Gal-1P values in patient 2 were normal after dietary intervention. In most CG patients, Gal-1P may decrease after initiation of the diet, but it usually does not normalize. In the report from the GalNet Registry, Gal-1P values were normal in 9% of neonatal CG patients [9]. Also, galactose in urine was initially normal in patient 2. These observations suggest that in a patient with a phenotype that strongly resembles CG, such as in patient 2 and 3, in which an initial biochemical test is negative, more than one biochemical test (Gal-1P, galactose or galactitol) or even genetic tests should be performed.

Lastly, the finding of an abnormal serum transferrin IEF in all patients may also suggest this diagnosis in the absence of a primary glycosylation disorder. In CG, the accumulation of galactose intermediates results in competitive inhibition of glycosyltransferases [13,23]. Also, a shortage of end-product UDP-hexose sugars may disrupt galactosylation/glycosylation of proteins and lipids [13,24]. Therefore, CG has been considered a secondary disorder of glycosylation. Both defects in glycan assembly and processing have been observed in CG and patients may show a CDG-1 or 2 pattern as observed in our patients [12,13,16]. Patients with CG and some CDG share many clinical characteristics such as intellectual disability, liver disease, coagulopathy, failure to thrive and frequent infections. Especially in patient 1, the

phenotype of the first month with hypotonia, failure to thrive, diarrhea, and lethargy was similar to that of a neonatal PMM2-CDG presentation [10] . These observations suggest that in patients with a suspicion of CDG, CG should also be considered.

A very early diagnosis, such as by neonatal screening and institution of diet is important as timely diet initiation is a favorable prognostic factor [9].

In conclusion, we describe the natural history of three late-diagnosed patients with CG. It illustrates the difficulties and pitfalls of timely diagnosing CG. The late diagnosis of these patients underlines the added value of neonatal CG screening. Moreover, late-onset (clinical) manifestations should prompt further diagnostic testing.

## Ethics statement

Research on patients' DNA was approved by the Ethical Committees. Legal guardians of all patients detailed in this paper provided written informed consent.

## Author contributions

Dulce Quelhas – Conceptual design study, writing, literature searching. Sandra D.K. Kingma – Data analysis and collaboration in paper writing. An I. Jonckheere – Collaboration in writing.. Claudia S. Smeets-Peels – Collaboration in data analysis. Daniel Costa Gomes – Collaboration in clinical data collection and analysis José Duro – Collaboration in clinical data collection and analysis. Anabela Oliveira – Collaboration in critical review. Gert Matthijs – Collaboration in molecular analysis and review. Laura K.M. Steinbusch – Collaboration in critical review. Jaak Jaeken – Initiator, Conceptual design study, collaboration in writing, data analysis and critical review. Isabel Rivera - Collaboration in biochemical analysis and critical review. Estela Rubio-Gozalbo - Critical review and writing.

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## Authors declaration

All authors declare that there is no conflict of interest, and that this manuscript has not been/will not be submitted elsewhere.

## CRediT authorship contribution statement

**Dulce Quelhas:** Conceptualization, Writing – original draft. **Sandra D.K. Kingma:** Data curation, Writing – original draft. **An I. Jonckheere:** Writing – original draft. **Claudia S. Smeets-Peels:** Data curation. **Daniel Costa Gomes:** Data curation. **José Duro:** Data curation. **Anabela Oliveira:** Writing – review & editing. **Gert Matthijs:** Investigation. **Laura K.M. Steinbusch:** Writing – review & editing. **Jaak Jaeken:** Conceptualization, Writing – original draft. **Isabel Rivera:** Investigation. **Estela Rubio-Gozalbo:** Writing – review & editing.

## Declaration of competing interest

None.

## Data availability

Data will be made available on request.

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