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# Untreated Classic Galactosemia: A Rare Cause of Adult-Onset Progressive Cerebellar Ataxia – A Case Report

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**Keywords**
Cerebellar ataxia · Tremor · Classic galactosemia · Carbohydrate-deficient transferrin · Case report

**Abstract**
***Introduction:*** Identifying the underlying etiology of nonfamilial adult-onset progressive cerebellar ataxia is often challenging because neurologists must consider almost all nongenetic and genetic causes of ataxia. ***Case Presentation:*** A 39-year-old woman was hospitalized for progressive ataxia with pyramidal and cognitive dysfunction after a right arm shaking and coordination problem deteriorated progressively over 1.5 years. The patient's medical history included amenorrhea, cataracts, developmental delays, consanguinity of the parents, motor coordination issues, and diarrhea and vomiting in infancy. An important finding that enabled us to solve the diagnostic conundrum was the elevated carbohydrate-deficient transferrin levels in the lack of alcohol-related symptoms, which also occur in untreated carbohydrate metabolism disorders, sometimes with ataxia as a leading symptom. The decreased erythrocyte galactose-1-phosphate uridyltransferase (GALT) enzyme activity and the elevated erythrocyte galactose-1-phosphate (Gal-1P) concentration led to the final diagnosis of galactosemia, a rare metabolic disorder. The patient's condition stayed stable with strict adherence to lactose-free and galactose-restricted diets, regular physiotherapy, and speech therapy, despite attempts to control the crippling tremor. ***Conclusion:*** This case highlights the importance of considering rare diseases based on unexplained clinical and laboratory findings. Newborn screening does not change the long-term complications of early-treated classical galactosemia. A small percentage of these patients develop ataxia tremor syndrome.



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## Introduction

Ataxias, characterized mainly by balance, coordination, and speech impairment, can occasionally be combined with extrapyramidal movement disorders, pyramidal signs, cognitive-affective symptoms, seizures, and peripheral neuropathy [1]. Sporadic adult-onset ataxias are particularly challenging due to the need to consider all nongenetic and genetic causes.

Classic galactosemia, a rare autosomal recessive inherited disorder of galactose metabolism, is caused by a severe GALT deficiency [2]. Galactose (milk) consumption in newborns with galactosemia leads to Gal-1P accumulation, metabolites, and multi-organ failure. Thus, galactose-restricted and lactose-free diets are lifesaving when initiated early. Nevertheless, many patients develop long-term complications, such as cerebellar ataxia, tremor, speech or language deficits, ovarian failure, and cataracts, despite adherence to dietary galactose restrictions [3–5].

Herein, we emphasize the role of a systematic approach in patients presenting with progressive adult-onset cerebellar ataxia. A reasonable diagnosis can frequently be reached from the minor details in the history, the clinical examination, and the easily accessible laboratory tests.

## Case Presentation

In January 2019, a 39-year-old right-handed woman from a European country presented to our department with a 1.5-year history of deteriorating right arm shaking and coordination. She reported limitations in almost all activities of daily living involving her right hand, which forced her to use her left hand mainly; she did not complain about walking difficulties or falls. She experienced learning difficulties and was later diagnosed with cataracts in the right eye and secondary amenorrhea. In addition, the patient's sister reported hospitalization a few days after birth (without complications) because of diarrhea and vomiting, which responded well to the strict temporary consumption of lactose-free milk (without a formal diagnosis). She was otherwise healthy, did not follow a lactose/galactose-restricted diet in adulthood, and had no family history of neurological disease, although she reported that her parents were consanguine.

Neurological examination revealed a persisting, postural, and intentional tremor of the dominant upper extremity, hypermetria with overshooting upon release, hyperreflexia with bilateral positive Babinski's sign, gait ataxia, slight dysarthria, square-wave jerks, but no other abnormal eye movements. Pouring water between cups was only possible by adduction of the right arm against the body and flection of the elbow to partly suppress tremor activity. Anyhow, it led to a massive spillage of water. Other relieving factors or triggers were neither noted nor reported. We did not notice rest tremor. Furthermore, the Montreal Cognitive Assessment test indicated mild deficits in visuospatial and executive function and recall memory (21/30 points).

Based on the patient's history and physical findings, we postulated an adult-onset progressive cerebellar ataxia with pyramidal and cognitive dysfunction. We then performed a three-stage diagnostic evaluation (Table 1, partly performed by the referring neurologist), which yielded no clear explanation of the patient's symptoms. The laboratory tests were performed according to the recommendations of the German Neurological Society for the workup and management of Ataxias [6]. Our investigation revealed two key findings. Brain magnetic resonance imaging showed mild frontal lobe cortical atrophy and diffuse hyperintense lesions in the centrum semiovale and the pons (Fig. 1a, b). Second,

carbohydrate-deficient transferrin (CDT) levels were more than three times the upper limit of normal (disialo-transferrin 5.68 [<1.7] %). However, the patient denied alcohol consumption.

Considering the patient's medical history (neonatal diarrhea and vomiting, cataracts, amenorrhea, cognitive difficulties, motor coordination problems, and parental consanguinity) and the secondary CDT elevation in untreated carbohydrate metabolism disorders, we assumed galactosemia to be the most likely diagnosis. We then confirmed our hypothesis by detection of elevated erythrocyte Gal-1P concentration (3.47 [0.18–0.57] mg/dL) and reduced erythrocyte GALT enzyme activity (1.0 [21.3–38.4] μmol/h/g hemoglobin), whereas plasma galactose was 0.01 (<0.27) mmol/L. Liver function test results were normal [alanine transaminase, 14 (<35) IU/L; aspartate transaminase, 22 (<35) IU/L; and alkaline phosphatase 75 (35–104) IU/L]. Clinicians should confirm the diagnosis of classical galactosemia by measuring GALT enzyme activity in red blood cells (absent or significantly decreased) and/or GALT gene analysis, per the International Clinical Guideline for the Management of Classical Galactosemia [3]. In this clear situation, we decided not to perform genetic testing.

The patient and her relatives were informed about the disease in detail. The patient's condition remained stable with strict adherence to the recommended galactose-restricted and lactose-free diets, regular physiotherapy, and speech therapy. Attempts to control her debilitating tremor using propranolol, topiramate, and clonazepam were unsuccessful. Nevertheless, with dietary treatment, Gal-1P levels were reduced, but consistently over 1 mg/dL (1.92 and 2.85 [0.18–0.57] mg/dL, August 2022), whereas plasma galactose was <0.1 (<0.27) mmol/L, and CDT levels returned to normal. This constellation and the clinical course with primary ovarian insufficiency suggested classical galactosemia rather than clinical variant galactosemia.

## Discussion

Herein, we describe a case of adult-onset cerebellar ataxia with other motor and cognitive symptoms. Interestingly, our patient's medical history and secondarily altered CDT suggested galactosemia at the age of 39 years. The patient was born in a country that does not perform galactosemia newborn screening. What diagnosis was made in the newborn period in the context of vomiting remains unknown. Up to one-third of patients with classical galactosemia have motor symptoms such as tremor, ataxia, and dystonia, which may benefit from appropriate symptomatic treatment [10, 11]. Neurocognitive symptoms include language production and speech impairments, slower information processing, memory and executive functioning deficits, and an overall lower intelligence level [2, 3, 12, 13]. The patient's pyramidal and neurocognitive symptoms could be attributed to frontal lobe atrophy and white matter changes, as displayed on the brain magnetic resonance imaging (Fig. 1a). In contrast, we found no apparent structural correlates of cerebellar symptoms (Fig. 1b). Previous studies have described similar radiological findings and variable cerebellar changes, possibly due to alterations in myelination [14, 15].

A key finding that helped us solve the diagnostic puzzle was the elevated CDT levels in the absence of other alcohol-associated stigmata. CDT is a standardized alcohol biomarker [16] because chronic alcohol intake interferes with protein glycosylation, a multi-enzymatic process that is crucial for adequate protein function [17]. However, galactosemia, fructosemia, and almost 50 other congenital disorders can lead to abnormal glycosylation patterns and elevated levels of CDT [18–21].

Based on previous reviews of adult-onset sporadic ataxia [7, 8], we outlined the possible differential diagnoses evaluated in our patient (Table 1), three of which we would like to highlight because of their common cerebellar, pyramidal, and cognitive symptoms. In Alexander's disease, caused by a glial fibrillary acidic protein mutation, the onset can occur as

**Table 1.** Possible etiologies for symptomatology evaluated in our patient and diagnostic tests performed

| | | |
|---|---|---|
| Stage 1 | Structural | MRI of the brain and spine with contrast |
| | Nonstructural | CSF testing* |
| | Neoplastic | CBC, SPEP, IF, UPEP, CT chest/abdomen/pelvis, transvaginal US, mammography |
| | Toxic, metabolic | Electrolytes, renal/liver function, CK, CDT |
| | Endocrine, nutritional | TSH, HbA1c, Vitamin B1, B12, and E |
| | Infectious | HIV, EBV, VZV, HBV, HCV, RPR, Lyme |
| | Inflammatory, autoimmune, paraneoplastic | ANA, ANCA, LA, ACA, SSA/SSB, ACE, anti-TPO, TG, antineuronal antibodies** |
| Stage 2 | Celiac disease | Anti-gliadin, -endomysial, and -TTG antibody |
| | Ataxia-telangiectasia, ataxia with oculomotor apraxia | Alpha-fetoprotein, fasting lipids |
| | Wilson disease, aceruloplasminemia | Copper, ceruloplasmin |
| | Refsum disease | Phytanic acid |
| | Cerebrotendinous xanthomatosis | Cholestanol, 7αC4 |
| | Adrenoleukodystrophy | Very long-chain fatty acids |
| | Niemann-Pick disease type C | Oxysterol |
| Stage 3 | Optic and peripheral neuropathies | VEP, NCS |
| | Mitochondrial cytopathies | Lactate, pyruvate, SATET |
| | | Genetic testing (not performed in our patient) |
| | | Further possible tests see references [1, 7–9] |

MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; CBC, complete blood count; SPEP, serum protein electrophoresis; IF, immunofixation; UPEP, urine protein electrophoresis; CT, computed tomography; US, ultrasound; CK, creatine kinase; CDT, carbohydrate-deficient transferrin; TSH, thyroid-stimulating hormone; HbA1c, hemoglobin A1c; HIV, human immunodeficiency virus; EBV, Epstein-Barr Virus; VZV, varicella zoster virus; HBV, hepatitis B virus; HCV, hepatitis C virus; RPR, rapid plasma reagin; ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasmic antibodies; LA, lupus anticoagulant; aCL, anticardiolipin antibodies; SSA/SSB, Sjögren's disease A and B; ACE, angiotensin-converting enzyme; TPO, thyroid peroxidase; TG, Thyroglobulin; TTG, tissue transglutaminase; 7αC4, 7-alpha-hydroxy-4-cholesten-3-one; VEP, visual evoked potentials; NCS, nerve conduction studies; SATET, sub-anaerobic threshold exercise test. *CSF testing included cell count, protein, glucose, immunoglobulin G synthesis rate and index, oligoclonal bands, cultures, cytology, and antineuronal antibodies. **Antineuronal antibodies included anti-N-methyl-D-aspartate receptor (NMDAR), anti-contactin-associated protein-like 2 (CASPR-2), antiglutamic acid decarboxylase (GAD), anti-γ-aminobutyric acid receptors ($GABA_AR$ and $GABA_BR$), anti-Yo, anti-Hu, anti-Tr, anti-Ri, anti-Ma, anti-Purkinje cell antibody type 2 (PCA-2), and others.

late as 62 years of age with progressive ataxia and pyramidal signs [22]. However, our patient's profile lacked other typical findings such as palatal tremor, bulbar palsy, or medulla oblongata atrophy. Second, Niemann-Pick-type C (NPC), a lysosomal storage disorder caused by NPC1 or NPC2 gene mutations, can also occur in adulthood with ataxia, cognitive decline, and cortical or cerebellar atrophy [23]. Nevertheless, we did not observe other distinguishing characteristics, including dysphagia, seizures, vertical supranuclear gaze palsy, psychosis, or depression [24]. Third, spinocerebellar ataxia (SCA) can present as sporadic ataxia, even though it has an autosomal dominant inheritance. However, the relatively rapid neurological progression, in combination with the lack of cerebellar degeneration on imaging, made this diagnosis rather unlikely [25–27].

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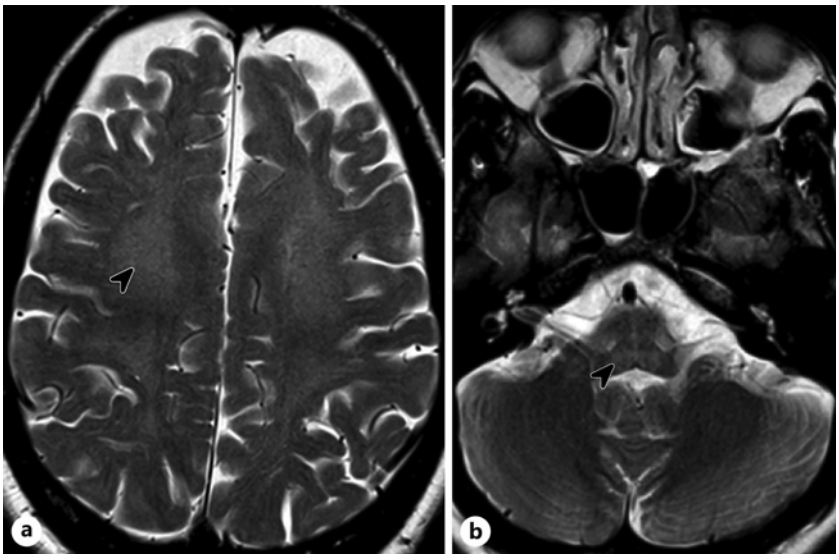


**Fig. 1.** Axial T2w images of brain magnetic resonance imaging (MRI): frontal lobe cortical atrophy and diffuse hyperintense lesions in centrum semiovale and periventricular areas (**a**), as well as in pons without signs of cerebellar atrophy (**b**).

Another valuable clue to diagnosis was the association of ovarian failure with a movement disorder described in only a few diseases, namely galactosemia, leukodystrophy with vanishing white matter (VWM), and fragile X-associated tremor/ataxia syndrome (FXTAS) [28]. The late-onset-form of VWM resulting from a mutation in one of the five eukaryotic initiation factor 2 B genes (EIF2B1-5) can present with spastic paraparesis, cerebellar ataxia, depression, schizophrenia, primary ovarian failure, and cerebral atrophy; however, the typical vanishing of white matter can be absent [29]. FTXAS, consisting of progressive intention tremor, gait ataxia, parkinsonism, and autonomic dysfunction, is rarely seen in female carriers of a premutation in the fragile X mental retardation 1 (*FMR1*) gene and may be accompanied by mild cognitive and behavioral deficits or premature ovarian failure [30–33]. Early involvement of experts and appropriate use of software tools like the "Phenomizer" [34, 35] can assist clinicians in navigating the complex landscape of rare neurometabolic disorders and provide valuable advice to the differential diagnosis before ordering more tenuous or costly investigations.

We would also like to emphasize the importance of early diagnosis and patient education regarding galactosemia. Newborn screening implemented in most countries and a galactose-restricted diet in the first week of life can resolve acute neonatal illness with hepato-, coagulo-, encephalopathy, and cataracts [2]. However, complications affecting the central nervous and female reproductive systems develop later in life. Patients and families must be counseled, understand the disease and nutritional therapy, and receive tailored follow-ups, especially for female patients, to assess pubertal development and neurodevelopmental impairments. Interestingly, there is controversy regarding how strictly a galactose-restricted diet should be adhered to, particularly in adulthood [2, 36, 37]. However, current international galactosemia guidelines still recommend a lifelong galactose-restricted diet [9]. Our patient admitted that she had followed a special diet for a limited period because she had never considered that her "milk allergy" or less strict adherence to the diet could have detrimental effects on her health.

In conclusion, although this case report does not describe a novelty or help generate a new research hypothesis, it still holds solid educational value. The narrative aspect of our case

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provides an in-depth understanding of the neurological complications of a rare neurometabolic disorder presenting later in life with a phenotype primarily observed years ago. Moreover, the diagnostic assessment illustrated above and shown in Table 1 can be used as a structured approach to evaluate patients with cerebellar ataxia. Routine laboratory tests, such as the measurement of CDT, may give valuable diagnostic insight into this process. However, in cases of unusual clinical constellations, early involvement of specialists can lead to a faster diagnosis of rare diseases. The CARE Checklist has been completed by the authors for this case report, attached as supplementary material.

## Patient's Perspective

A few days after my birth, my family told me I had to go to the hospital with severe vomiting and diarrhea. Relatives told me, doctors found a minor brain injury due to an allergy to lactose but did not provide detailed information to my parents. They told me later after a month's stay and strict consumption of lactose-free milk, I made a remarkable recovery and could return home. When I started school, I faced my first problems with reading and writing, and when I was 8 years old, my teachers told my parents that I could not meet the expected school performance standards for my age. At the age of 13, I had an irregular menstrual cycle. A gynecologist concluded that the brain injury was the cause of the problem and prescribed a hormonal pill. I was under regular medical supervision for the following 3 years and a diet excluding lactose. Since then, I have had an everyday life and did not follow a lactose-free diet in adulthood. The only thing one could notice was that I was a little slower than the others. I did not think the "milk allergy" could cause any more problems until I started shaking badly this year.

## Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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## Author Contributions

All authors were responsible for the clinical management of the patient. I. Karafyllis wrote the manuscript. J.M. Nuoffer, J.P. Michelis, and L. Chilver-Stainer helped draft the manuscript. All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

## Data Availability Statement

Data sharing was not applicable to this study because no datasets were generated or analyzed. All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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