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Case Report

# Expanding the phenotype of RBCK1-associated polyglucosan body myopathy type 1

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ABSTRACT

Polyglucosan body myopathy-1 (PGBM1) is an extremely rare glycogen storage diseases that leads to muscle weakness and cardiomyopathy due to the accumulation of polyglucosan bodies. The clinical presentation appears to be partially dependent on the genetic mutation, but no clear genotype/phenotype correlation is currently possible.

We describe a 7 year old patient, who initially presented with recurrent vomiting and respiratory infections until her first year of life. Diagnostic workup revealed an achalasia and the whole exome sequencing revealed an homozygous *RBCK1* (*RANBP2-type and C3HC4-type zinc finger containing 1*) variant (c.896_899delAGTG) located in exon 7 (mid-domain), which has also been described in 4 patients with PGBM1.

The unusual presentation with gastrointestinal and respiratory symptoms before the development of progressive muscle weakness expands the phenotype of this disease.

## 1. Introduction

*RBCK1*-associated polyglucosan body myopathy-1 (PGBM1), with or without immunodeficiency, is an autosomal recessive disorder that causes skeletal muscle weakness and cardiomyopathy due to the pathological accumulation of polyglucosan bodies [1].RBCK1 (also known as haem-oxidised IRP2 ubiquitin ligase-1)ensures the structural integrity of the linear ubiquitin chain assembly complex (LUBAC) and may play a role in the ubiquitination process of linear glycogen molecules, potentially triggering their removal from cells before toxic polyglucosan deposition occurs [2].

In a mouse model downregulation of glycogen synthase led to a reduction in glycogen levels and prevented the formation of polyglucosan bodies [3].In addition LUBAC acts as a regulator of NF-kB, which is a family of transcription factors involved in the immune response [4,5].

Our case report focuses on a patient with PGBM1 carrying a homozygous variant in the middle part of the *RBCK1* gene who initially presented with achalasia, which was complicated by failure to thrive and recurrent infections and later developed limb-girdle weakness. We would like to discuss the phenotype/genotype of our patient in relation to the literature and highlight that an accurate genotype-phenotype correlation in patients with this disease is currently not possible.

## 2. Case report

Here we report on a patient, now 7 years old of non-consanguineous parents, who was referred to a paediatric surgery unit at the age of 18 months because of recurrent vomiting that had started a few weeks after birth. A diagnostic work-up revealed a functional motility disorder and narrowing of the lower third of the oesophagus. A manometric diagnosis of achalasia was made and the patient underwent two bougienage procedures and a balloon dilatation as her parents refused a Heller myotomy. After these procedures, the patient was able to eat and drink slowly without vomiting and gained weight steadily, but she was still below the 3rd percentile for weight for age.

Because of recurrent bronchial and pulmonary infections, a lung examination was performed, which revealed atelectasis, bronchiectasis and bronchiolytic changes, as well as an increase in lymphoid tissue in the posterior mediastinum and hilar region (Fig. 1). Although the

*Abbreviations:* PGBM1, polyglucosan body myopathy-1; RBCK1, RANBP2-type and C3HC4-type zinc finger containing 1; EYA1, EYA transcriptional coactivator and phosphatase 1; NF-kB, nuclear factor k-light-chain-enhancer of activated B cells; CFTR, cystic fibrosis transmembrane conductance regulator.

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barium swallow study showed no aspiration, this cannot be completely ruled out as a cause for the pulmonary abnormalities. A sweat test was performed to exclude cystic fibrosis, and due to a borderline result (49 mmol/L), the diagnostic workup was extended to include whole-exome sequencing to detect variants in the CTFR gene and to avoid overlooking other causes due to the unclear clinical picture.

The test revealed a homozygous *RBCK1* variant c.896_899delAGTG, which is located in exon 7 (mid-domain) and causes a reading frame shift resulting in a premature termination signal after 45 amino acid changes. The expected effect is degradation of the mRNA by nonsense-mediated decay or a truncated protein (p.Glu 299Valfs *46). According to the ACMG consensus recommendations, the variant is classified as pathogenic (class 5) and is also listed in the variant databases HGMD and ClinVar. The variant has been described as homozygous in patients with *RBCK1*-associated polyglucosan body myopathy-1 (PGBM1) and the patient was referred to our neuromuscular outpatient clinic [6,7].

On initial presentation at the age of 7 years, the patient had a poor nutritional status, weighing only 17 kg (<1st percentile), with a height of 116.3 cm (5th percentile) and a BMI of 12.6 kg/m$^2$ (5th percentile).

On clinical examination the patient had limb girdle weakness, particularly of the hip and thigh muscles, with a Medical Research Council scale score of 4 in these particular muscle groups, and mild trunk hypotonia. As a result, she had difficulty rising from the floor, which required a clear Gowers' manoeuvre, and sitting up from a supine position. She was also slow to walk and climb stairs.

Routine blood sampling on initial presentation to the neuromuscular outpatient clinic revealed an elevated NT-proBNP of 489 ng/L (range 0–145 ng/L), probably the first sign of hypertrophic cardiomyopathy, and mildly elevated AST and ALT levels with normal CK levels, without evidence of cardiomyopathy or impaired cardiac function on electrocardiography and echocardiography, with left ventricular fractional shortening of 36.6%. In view of the recurrent infections and the elevated inflammatory parameters, a detailed work up for possible immunodeficiencies and autoimmune diseases was performed, with lymphocyte typing showing only signs of inflammation (lymphocytosis of B cells and helper T cells) and a normal functional test, which unfortunately could only be assessed to a limited extent due to the lack of vaccinations. In addition, an abdominal ultrasound showed a slightly enlarged liver and reactive mesenteric lymph nodes. The patient also had mild restrictive respiratory failure with a vital capacity of 74% and a forced expiratory volume in one second of 72%.

She is currently receiving multidisciplinary care coordinated by the neuromuscular outpatient clinic. In addition to inhaled bronchodilators and 3% sodium chloride, the patient receives regular physiotherapy to improve respiratory and motor function. Clinical follow-up, including echocardiography, and pulmonary function testing are conducted every six months. Dietary advice is planned.

## 3. Discussion

This case report describes a 7-year-old patient with PGBM1 related to RBCK1 deficiency. The girl initially presented with achalasia, which was complicated by failure to thrive and recurrent infections and later developed limb girdle muscle weakness. There was no evidence of cardiomyopathy on echocardiography, but NT-proBNP was slightly elevated.

Individuals with *RBCK1* variants show a range of manifestations, with different clinical phenotypes prevailing. Some people have muscle involvement, which is considered to be the hallmark of the disease, while others have immune system dysfunction. The exact reason for this wide clinical spectrum is still not fully understood.

However, as RBCK1 is a regulator of the NF-kB pathway, variants, particularly in the N-terminal region, may predispose to immunodeficiency and autoinflammation [4,5,8]. Boisson et al. reported three patients with an autoinflammatory phenotype and a high susceptibility to invasive pyogenic bacterial disease leading to early death. The authors demonstrated an impairment of NF-κB activation in fibroblasts and a hyper-responsiveness of mononuclear leukocytes to interleukin-1β in these patients [8]. On the other hand, Nilsson et al. showed that variants in the middle or C-terminal regions of *RBCK1* are more frequently associated with the myopathic subset of symptoms [6]. The onset and progression of weakness is very heterogeneous and most patients develop cardiomyopathy, which is the major life-limiting factor, apart from severe infections in immunocompromised patients [6,8]. Unfortunately there does not seem to be an exact genotype-phenotype correlation, as cases with PGBM1 and immunological dysfunction have also been described with variants outside the N-terminal part and missense variants seem to result in a milder disease course [6,7].

Only four other patients with exactly the same variant, c.896_899delAGTG located in exon 7 (mid-domain),have been reported in the literature [6,7]. Our patient presented with a mixed phenotype, similar in some aspects to the others, but with some differences

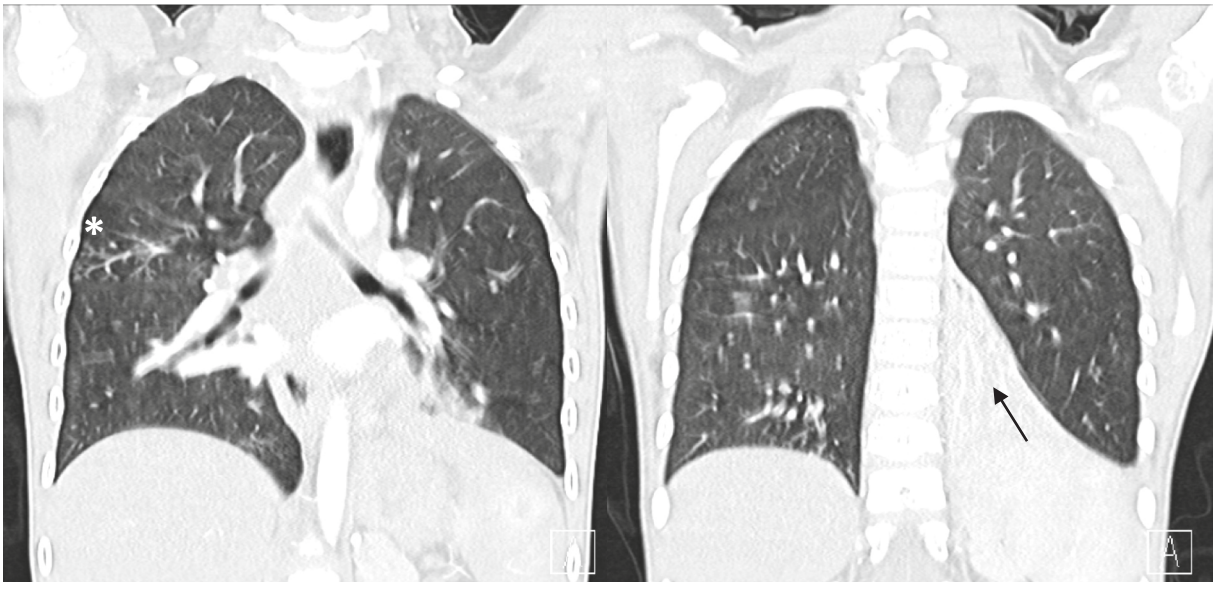

**Fig. 1.** Thorax computed tomography coronal images at the age of 6 years showing tree-in-bud sign (white star), atelectasis (black arrow) and bronchiectasis with mucoid impactions.

**Table 1**
Characteristics of our patient compared to four others carrying the same*RBCK1* variant (c.896_899delAGTG), which is located on exon 7 (mid-domain), in a homozygous state.

| | BIII:1 Nilsson et al. [6] | BIII:2 Nilsson et al. [6] | Patient I Krenn et al. [7] | Patient II Krenn et al. [7] | Our patient |
|---|---|---|---|---|---|
| Gender | Female | Male | Female | Female | Female |
| Age | 24 years (2013) | 19 years (2013) | Died at 17 years | 32 years (2017) | 7 years (2023) |
| Age at onset | 6 years | 5 years | 14 years | 12 years | 3 years |
| Initial symptoms | Leg weakness | Difficulty running | Dyspnea | Dyspnea | Recurrent infections |
| Weakness | Lower limbs | Lower limbs | Lower limbs | All four limbs | All four limbs |
| Ability to walk | Yes | Yes | Yes | No (wheelchair) | Yes |
| Cardiomyopathy | Yes (transplant at 14 years) | Yes (transplant at 13 years) | Yes | Yes (transplant at 17 years) | No |
| Elevated CK | X5 | X6 | X3 | X6 | Normal |
| Failure to thrive | Yes | Yes | N/A | N/A | Yes |
| Recurrent infections | No | No | Yes | Yes | Yes |
| Autoinflammation | No | No | ANA increased | Sweet's syndrome | No |
| Elevated ALT | Yes | Yes | N/A | N/A | Yes |
| Origin | N/A | N/A | Turkish | Austrian | Austrian |

*CK,* creatine kinase; *ANA,* antinuclear antibodies; *ALT,* alanine transaminase; *N/A,* not applicable.

(Table 1). One point is the normal CK-level in our patient compared to the others and no evidence of cardiomyopathy yet on echocardiography yet, but elevated NT-proBNP levels. The other four reported patients had cardiac complications leading to transplantation or death in adolescence. Close cardiological follow-up is therefore essential, and we are considering the use of cardiac MRI with T1-mapping and late gadolinium enhancement, similar to that used in Duchenne patients, for earlier detection of myocardial fibrosis [9].

It is not yet fully understood whether polyglucosan bodies can also accumulate in the central or peripheral nervous system and thus cause achalasia. However, a recent study revealed that in a mouse model the amylopectinosis of RBCK1 deficiency affects the brain, especially hippocampus, cerebellum and central spinal cord, similar to adult polyglucosan body disease and Lafora disease [3].

Due to the wide phenotypic spectrum and the rarity of this disease, it is still difficult to give an accurate prognosis for each individual case. Therefore, early genetic clarification seems to be all the more important to identify these patients and, with an increasing number of cases, to possibly be able to make a more precise statement about the course of the disease based on the type of variant.

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## CRediT authorship contribution statement

**Manuel Pühringer:** Conceptualization, Data curation, Writing – original draft. **Astrid Eisenkölbl:** Writing – review & editing. **Gudrun Gröppel:** Conceptualization, Methodology, Project administration, Supervision, Writing – review & editing.

## Declaration of Competing Interest

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report. We certify that the submission is original work and is not under review at any other publication.

## Data availability

No data was used for the research described in the article.

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