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# A Rehabilitation Journey with Pelizaeus-Merzbacher Disease (PMD)

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## ABSTRACT

*Pelizaeus-Merzbacher Disease (PMD) is a rare X-linked recessive leukodystrophy involving mutations in the proteolipid protein 1 (PLP1) gene. PMD can be classified into three subtypes based on severity; connatal (type I), transitional (type II), and classic (type III), with spastic paraplegia type 2 (SPG2) often considered a mild form of PMD. Life expectancy of PMD patients varies depending on the subtype, in which classic PMD, the most common phenotype, has a life expectancy around young adulthood. There is a paucity of reports on PMD given the rarity of the condition. We describe the disease progression of a 32-year-old male classic PMD patient with gene mutation c.56T>C in exon 2 of the PLP1 gene. The patient presented symptoms within his infancy, with a progressive decline in psychomotor and cognitive function. Despite close follow up, he was only diagnosed with PMD at the age of 18 following a brain MRI and genotyping.*

**Keywords**

Pelizaeus-Merzbacher Disease, Mutations, PLP1.

## Background

Pelizaeus-Merzbacher Disease (PMD) describes a spectrum of rare X-linked recessive leukodystrophies related to proteolipid protein 1 (PLP1) abnormalities [1]. PMD has an international prevalence ranging from 1:90,000–1:750,000 births, dependent on the ethnic demographic [2]. This leukodystrophy condition results from mutations in the PLP1 gene, in which PLP1 is the most abundant protein of CNS myelin [2,3]. Consequently, different mutations to the PLP1 gene results in varying degrees of hypomyelination of the CNS, producing a spectrum of PMD symptom severity, allowing for a classification of different PMD phenotypes [3]. In order from most severe to mildest, PMD can be categorised as above mentioned 3, with spastic paraplegia type 2 (SPG2) considered a less severe form of PMD [2,3], in which there is often overlap in symptoms between these classifications [1,4,5].

The most common form is the classic PMD phenotype, which exists as a mild-moderate severity and is typically due to duplications of the PLP1 gene [6]. While the pathological mechanisms are not fully understood, it has been reported that overexpression of PLP results in myelin protein which cannot be used functionally, significantly reducing myelination and causing oligodendrocyte dysfunction [2]. Classic PMD patients usually present during the first year of life, with neonatal axial hypotonia, failure to meet motor milestones, and progressive severe spasticity [4]. However, they retain a certain degree of cognition and the ability to partially mobilise, with a life expectancy commonly between adolescence to young adulthood [2].

The most severe form is connatal PMD, which is typically due to missense mutations of the PLP1 gene [1], resulting in protein misfolding, failure to transport these proteins, and eventual oligodendrocyte toxicity [1,2]. As the name suggests, connatal PMD presents during neonatal life, initially with severe hypotonia, extrapyramidal signs and laryngeal stridor [1,7]. These patients have severe cognitive impairment and can rarely mobilise or speak, with death occurring in early childhood due to secondary complications but may live longer with attentive care [3,5].

There is then SPG2, an allelic condition most commonly due to deletions in the PLP1 gene, producing milder phenotypes [3,4].

Deletions lead to milder symptoms as there is no accumulations of misfolded proteins, having less oligodendrocyte toxicity and therefore lesser degrees of hypomyelination [2]. Patients usually present in the first decade of life with spastic paraparesis, ataxia, mild cognitive impairment, and autonomic dysfunction such as spastic urinary bladder [2,8].

Diagnosis of PMD is made through a combination of comprehensive history, clinical examination, genotyping, and the use of imaging techniques. MRI plays a crucial role in classification of PMD as it allows for detailed visualisation of hypomyelination making it possible to distinguish between PMD phenotypes [2]. Symptom severity correlates to the degree of hypomyelination, where severer PMD forms produce diffuse and confluent hypomyelination, while SPG2 shows less hypomyelination in a tigroid/patchy pattern [9]. Management of PMD is largely symptomatic relief and supportive as there is currently no definitive treatment [9].

We report a 32-year-old male with PMD from his early stages of the disease through to his young adult life. Despite close follow up since early childhood, a formal diagnosis of PMD was only made at the age of 18 years of age following an MRI brain and genotyping study, in which the patient reports he was given an initial prognosis of 7 years to live. His genotyping study revealed a missense mutation of c.56T>C in exon 2 of the PLP1 gene. Despite progressive worsening in spasticity, dysarthria & stuttering, and a decline in cognitive & behavioural function, the patient's condition has remained stable, with MRI imaging studies demonstrating no interval change over a 5-year period.

## Case Presentation

The patient was born at term from a normal pregnancy, being the first child of two with no significant family history. His parents observed that by the age of 1 the patient was not meeting gross and fine motor development milestones, noting he could only start walking from the age of 2. He also suffered from visual impairments, with both optic atrophy and extraocular dysfunction, requiring squint surgical correction in early childhood. The patient has had intellectual deficits since childhood, which continued to deteriorate. The patient developed spastic paraplegia by the age of 4, becoming largely wheelchair dependent and was later diagnosed with cerebral palsy at 4.5-years-old. By age 8, the patient had undergone numerous muscle and tendon lengthening surgeries of his lower limbs. At ages 10 and 12, the patient had 3D gait analyses, which suggested an underlying degenerative neurological condition, and the need for further extensive corrective surgery. However, MRI studies at that point in time did not suggest findings for progressive changes.

The patient's spasticity continued to worsen throughout adolescence, requiring Botulinum Toxin A (BTA) treatment at age 12. His visual acuity progressively deteriorated, such that by the age of 15 he was only capable of reading extremely large print and seeing outlines. His ability to walk progressively declined, wherein his spastic paraplegia worsened with significant scissoring and has been mostly wheelchair bound by age 15. He suffered from significant pain in both his knees due to the spasticity and begun a trial of baclofen to good effect. The patient started having sleep difficulties at age 15, and often suffered from persistent headaches due to sleep deprivation. The patient was commenced on diazepam nocte to assist with muscle spasms and sleep. His ability to speak became increasingly dysarthric, though comprehensible. The patient underwent speech pathology for several years but ceased due to minimal beneficial effect.

The patient has a complex psychosocial history, with his parents' separation, leaving his father as his primary carer. He suffered from a gradual decline in his mood, cognition, and behaviour, being frequently suspended from school for aggressive & impulsive behaviour. He was reported to have numerous episodes of self-harm and suicide attempts, as well harming those close to him. The patient was commenced on antipsychotics as well as antidepressants to manage his behaviour.

## Investigations

Prior to the age of 18, the patient was classified as legally blind, and had further brain imaging studies, which demonstrated diffuse increase in white matter high signal within the cerebral hemispheres, in keeping with a hypomyelination syndrome (Figure 1a). Given the patient's brain imaging findings and symptoms, formal genotyping investigations for PMD were performed. A missense mutation of c.56T>C in exon 2 of the PLP1 gene was found, causing an amino acid change in position 19 from leucine to proline. No PLP1 duplication was detected. These investigation findings and the patient's symptoms were in keeping with a classic PMD diagnosis.

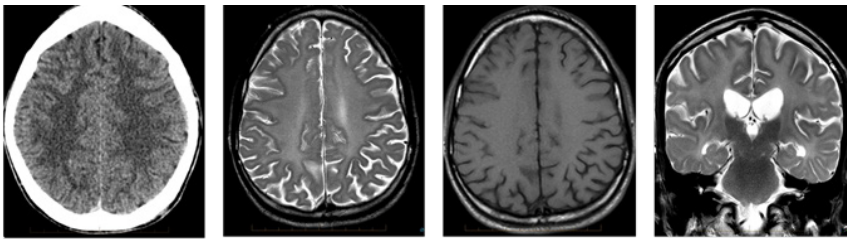


**Figure 1:** Representative axial and coronal slices of CT and MRI imaging of brain from 2009, 2016 to 2022. (1a) Initial axial non contrast CT obtained in 2009 (age 19), reveals diffuse confluent hypodensity in bilateral cerebral white matter; (1b) Axial MRI T2 weighted MRI in 2016 (age 27), reveals diffuse confluent symmetric increased signal in the cerebral white matter; and (1c) white matter signal abnormality is not evident on the axial T1 weighted sequence; (1d) Coronal T2-weighted MRI in 2022 (age 32), reveals similar diffuse hyperintense signal in supratentorial white matter.

## Treatment

Following his PMD diagnosis, at the age of 19, the patient transitioned from paediatric care to adult rehab services. He was commenced on regular medication for spasticity including clonazepam and baclofen. He initially had a good response to obturator nerve blocks and subsequent regular high dose BTA (upper to 700 units) treatment for his lower limb spasticity and maintained his goal of climbing stairs at his high set home for over 8 years.

## Outcome and follow up

By the age of 21, the patient begun to suffer from a neuropathic bladder and a neuropathic bowel, which has led to significant abdominal pain and haemorrhoids, whereby the patient punches his abdomen to force bowel motions to relieve his pain. He had multiple investigations including regular endoscopy and colonoscopy, which were all unremarkable. The patient underwent urodynamic studies at age 23, demonstrating poor bladder compliance with a slightly decreased bladder capacity. His neuropathic bladder has been managed with several medications, as well as intermittent self-catheterisation, though with issues of spending excessive periods of time on the toilet which is related to his anxiety and fear of having an accident in public. Additionally, due to continued improper use, the patient has suffered from many urinary tract infections requiring hospital admission.

From the age of 27, the patient began to develop new onset progressive upper motor neuron weakness in his upper limbs. MRI studies were performed at age 27, and after 5 years of worsening upper limb weakness (as well as other symptoms), another MRI was performed at age 32 to visualise the progression of PMD (Figure 1b, 1c, and 1d). These MRI studies did not demonstrate any significant interval changes over the 5 years, in which both reported comparable levels diffuse homogenous T2 hyperintensity in the cerebral white matter, with symmetrical incomplete myelination of the internal capsule. This makes it difficult to identify the exact cause of the patient's symptoms, though it is in keeping with the PMD disease course.

At age of 32, the patient has ongoing significant dysarthria & spastic paraplegia but is currently still capable of mobilising via wheelchair by himself, though he reportedly falls up to 5 times a day. He requires significant support when attempting to stand and is unable to take any unsupported steps. He continues intermittent self-catheterisation, with Botox injections to his bladder with modest therapeutic benefit. Though the patient's condition continues to deteriorate, he has managed to maintain recreational physical activities with a positive attitude, completing numerous hand cycling marathons for fundraisers for PMD. He continues his care under a multidisciplinary team, with regular rehabilitation physician, neurology, gastrointestinal, urology and psychiatric input.

## Discussion and Mini Literature Review

While our patient presented with classic PMD symptoms during infancy and was closely followed throughout childhood and adolescence, his diagnosis of PMD took many years. Depending on severity, classic PMD age of onset varies between 3 months and 9 years, and the age of death varies between 6 years and 25 years [10], though some report it is possible for milder cases to live up to their seventh decade of life [3]. Unfortunately, an earlier diagnosis may not have necessarily changed the patient's disease progression as there is no definitive treatment, and management is largely symptomatic relief [9].

While there is a lack of research on the rehabilitation of PMD patients, Jang et al. report a case of an infant with classic PMD receiving early intensive rehabilitation training over 3 months had improvements in gross and fine motor function [11]. In general, children with a neurological deficit, such as cerebral palsy, benefit significantly more in the first 2 years of life from rehabilitation than later in life [11]. This suggests intervention at an early stage of the disease progression can help PMD patients achieve optimal function and possible catch up in growth, though this is a single patient without long-term follow up and should not be generalised. Nonetheless, it is important to diagnose PMD as early as possible to allow for early rehabilitation and optimise function.

MRI plays an extremely crucial role in supporting a PMD diagnosis, which reveals diffuse hypomyelination with T2 hyperintensity in cerebral white matter [1-4,9]. Unfortunately, it has been reported that MRI findings may have no abnormalities in suspected PMD patients until the age of 2 [12], in which our patient's MRI brain did not show any abnormalities by age 12 despite progressive deterioration. Interestingly, while PMD patients have a progressive functional decline, there is no evidence that PMD causes progressive white matter destruction over time, but rather a defect in myelin formation/maturation [2]. This was in keeping with our patient's case, as no MRI changes were noted over a 5-year period.

We have noted that the patient suffers from a neuropathic bladder, which has not been frequently reported in classic PMD and is more commonly seen in complicated SPG2 [2,3]. However, SPG2 is less likely in our patient as Hudson suggests SPG2 patients should still be capable of ambulating for their entire life (albeit with a spastic gait) [3], as well as Cailloux et al. state that the SPG2 differs from the more severe PMD phenotypes in that motor milestone achievement is almost normal in the first year of life for SPG2 [13]. Our patient was incapable to ambulating from a very early age, with a failure to meet motor milestones during infancy. This is common for patients with classic PMD, in which they can temporarily walk during early childhood, but become wheelchair-bound due to progressive spastic paraplegia [4]. Furthermore, it has also been noted that SPG2 shows less severe abnormalities on MRI, only revealing a patchy/tigroid pattern of T2 hyperintensity rather than a diffuse hypomyelination like what was seen in our patient from adulthood [9].

## Conclusion

- PMD is rare and diagnosis may take many years, thus it is very important for physicians to closely track patient functional deterioration.

- There is a need for early genotyping studies for PMD when there is clinical suspicion.
- MRI findings may not demonstrate characteristic diffuse homogenous T2 hypomyelination during childhood despite symptom manifestation.
- Despite functional deterioration with time, ambulatory rehabilitation plays a role to mitigate disability and improve quality of life of patients with PMD.

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