CASE REPORT

Electrodiagnostic Findings in a Case of Pyle's Disease: A Case-Report

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ABSTRACT

Pyle's disease (PD), also known as metaphyseal dysplasia, is a rare genetic skeletal disorder characterized by a specific radiologic feature known as the Erlenmeyer-flask deformity, the expansion of trabecular metaphyses, specifically in the distal aspects of long bones. The main pathophysiology of this disease is caused by mutations in the Secreted Frizzled-Related Protein 4 (SFRP4) gene.

This case report aims to discuss the electrodiagnostic findings of an 8-year-old girl diagnosed with PD. This evaluation revealed normal sensory nerve action potentials (SNAP); however, compound muscle action potentials (CMAP) showed minimal amplitudes with increased latencies and profound reductions in nerve conduction velocities (NCVs), particularly in the lower limbs. These features are consistent with peripheral motor polyneuropathy with a mixed axonal and demyelinating pattern.

This case is reported because PD is an uncommon disorder, and until now, there has been no literature describing the electrodiagnostic features of this disease.

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Introduction

Pyle's disease (PD) was first described in 1931 as an unusual bone development by an American orthopedic surgeon, Edwin Pyle (1).

PD follows an autosomal recessive pattern of inheritance (2). The primary gene involved is Secreted Frizzled-Related Protein 4 (SFRP4), and any deletion of this gene leads to increased trabecular bone mass but reduced cortical bone thickness (3).

Clinical manifestations of PD include genu valgum, muscle weakness, joint pain, scoliosis, and restriction in elbow extension. Additionally, maxillofacial abnormalities such as poor dental implantation, malocclusion, and prognathism may accompany the disease (4).

The typical radiographic finding in PD is expanded trabecular metaphyses, specifically in the distal aspects of long bones, referred to as Erlenmeyer-flask deformity (EFD). While this deformity can be found in 20 rare conditions, it is prominent in PD, affecting all long bones (5). Other common radiological features include widening of proximal phalanges and distal metacarpal bones, cortical thinning, and mild cranial sclerosis (6).

The most similar differential diagnosis to PD is craniometaphyseal dysplasia. However, clinical, radiological findings, and genetic characteristics distinguish them as two distinct conditions (7). Additionally, no cranial nerve compression exists in PD, unlike in craniometaphyseal dysplasia. (8)

This study presents the case of an 8-year-old girl diagnosed with PD. Electrodiagnostic testing revealed peripheral motor polyneuropathy characterized by both axonal and demyelinating features, with more pronounced involvement in the lower limbs. To the best of our knowledge, this is the first report highlighting electrodiagnostic findings related to PD.

Case presentation

An 8-year-old Persian girl was admitted to the electrodiagnostic clinic of Amin Hospital in Isfahan,

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Iran, presenting with an out-toeing gait as the chief complaint.

The patient was delivered via normal vaginal delivery, reportedly two weeks earlier than the predicted date, estimated to be around 35 weeks of gestational age. The pregnancy and delivery were uneventful, according to her mother. The mother did not recall the exact milestones of sitting and standing independently. Nevertheless, she noted that her daughter began walking at 18 months and subsequently experienced a femoral fracture due to falling.

Table 1. Summary of CMAPs

Nerve / Sites	Muscle	Latency	Amplitude	Amp %	Distance	Lat Diff	Velocity
		ms	mV	%	mm	ms	m/s
Left median.APB							
Wrist	APB	2.92	1.8	100	70		
Elbow	APB	6.67	1.2	64.5	170	3.75	45
Right median.APB							
Wrist	APB	2.71	3.7	100	70		
Elbow	APB	6.30	1.8	48.3	165	3.59	46
Left ulnar.ADM							
Wrist	ADM	2.40	4.2	100	70		
B.Elbow	ADM	6.46	3.1	73.7	190	4.06	47
Right ulnar.ADM							
Wrist	ADM	2.29	3.4	100	70		
B.Elbow	ADM	5.73	2.7	77.5	170	3.44	49
L Peroneal - EDB							
Ankle	EDB	9.69	0.4	100	80		
Fib head	EDB	17.81	0.1	28.5	220	8.13	27
R Peroneal - EDB							
Ankle	EDB	8.75	0.9	100	80		
Fib head	EDB	20.31	0.4	40.6	245	11.56	21
L Tibial - AH							
Ankle	AH	7.24	0.6	100	80		
Pop fossa	AH	17.14	0.3	54.4	300	9.90	30
R Tibial - AH							
Ankle	AH	6.82	0.2	100	80		
Pop fossa	AH	17.29	0.2	79.8	295	10.47	28

The parents noticed the out-toeing gait over time, along with a disparity in activity level compared to peers, prompting consultations with healthcare professionals. The patient herself complained of feeling unsteady during physical activities, reporting frequent falls. However, she denied any sensory impairments or difficulties with proximal muscle activities such as combing hair or climbing stairs. No complaints of autonomic dysfunction, bowel or bladder issues, cervical, or low back pain were observed.

The patient was attending elementary school, performing academically at a level consistent with her peers. Fine motor skills, assessed through writing abilities, were within normal limits. The family denied a history of prolonged infections, head trauma, or other significant medical issues. The parents were consanguineous and had no other children. The routine urine and blood biochemistry tests for the parents were all within normal range. A maternal uncle had a history of lumbar spinal stenosis requiring surgery at age 40.

Upon physical examination, the patient exhibited an out-toeing gait, impaired heel walking, bilateral genuvalgum and genurecruvatum along with an increased carrying angle in both elbows. Dental irregularities were observed, but speech and voice were normal. Mild scoliosis was detected after Adams testing.

The physical exam of cranial nerves was normal; however, she had a horizontal nystagmus.

The sensory exam and strength of both proximal and distal muscles were normal and symmetrical.

The reflexes of the upper limbs were normal, but both patellar reflexes were hypo (+1), and the ankle reflex was undetectable.

Babanski and Hoffman's signs were negative. The finger-to-nose test was normal. Furthermore, the Romberg’s sign and Gowers’ sign yielded negative results.

The blood CPK was within normal range, measuring 98.5.

Paraclinical imaging investigations, including brain and lumbosacral magnetic resonance imaging (MRI), were normal. The performed X-rays were consistent with brachycephaly and increased Talo-Calcaneal angle. Furthermore, the X-rays of all long bones were consistent with EFD. (Figure 1)

Gene analysis was requested for both the patient and her parents. The analysis revealed a heterozygous missense variation in the SFRP4 gene (c.314G>C; p.Arg105Pro) in both parents, while the patient’s

MLPA analysis did not detect any deletions or duplications in the DMD gene. Given that Pyle disease follows an autosomal recessive inheritance pattern, the patient is likely homozygous or compound heterozygous for the mutation, leading to the observed phenotype.

Amino acid profiles in both plasma and urine revealed no abnormality. The acylcarnitine profile was also normal.

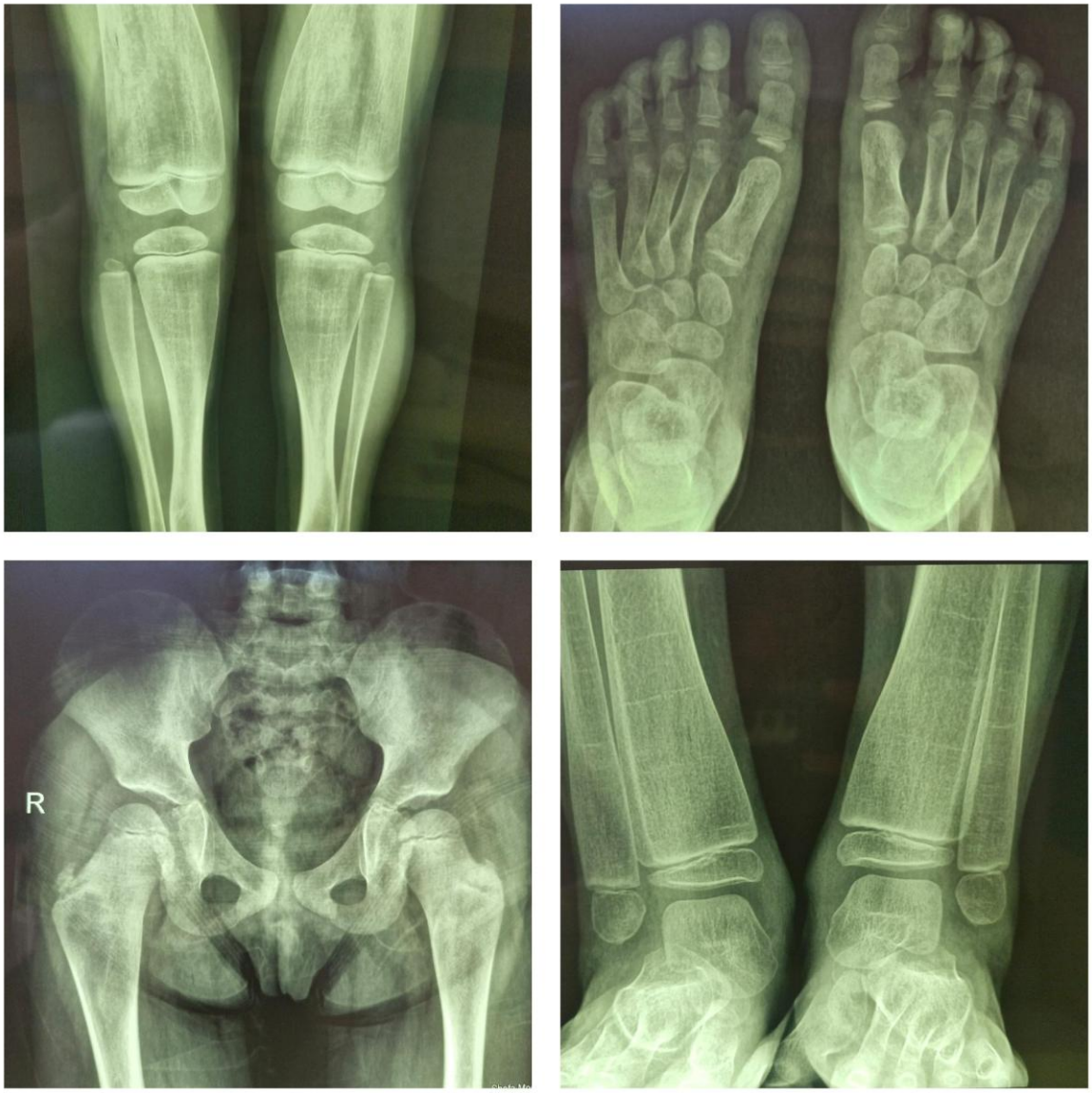

Figure 1. X-rays of lower limbs in a pediatric case of Pyle disease

The electrodiagnostic evaluation, encompassing nerve conduction studies (NCS) and electromyography (EMG), was done. The NCS was recorded via a standard bar electrode, and for EMG, the concentric needle was used. This study tested all routine sensory and motor nerves in both upper and lower extremities, yielding the following results:

1. All tested sensory nerve action potentials (SNAP) were normal in both amplitudes and latencies.

2. As shown in Table 1, compound muscle action potentials (CMAPs) exhibited minimal amplitudes, particularly in the lower limbs, along with increased latencies and profound reductions in nerve conduction velocities (NCVs). Additionally, in some nerves, a significant reduction in CMAP amplitude between distal and proximal stimulation sites was observed, consistent with conduction block.

EMG in all tested muscles exhibited a neurogenic pattern, with more severity in distal muscles compared to proximal ones, but revealed no evidence of denervation.

The F waves were either absent or very late, and H reflexes of the gastrocnemius muscles were undetectable.

These findings are suggestive of peripheral motor polyneuropathy, with a mixed axonal and demyelinating pattern and more severe involvement of the lower limbs.

Discussion

Pyle's metaphyseal dysplasia is an uncommon genetic disorder, occurring in less than one case per million people. Since most cases are asymptomatic, diagnosis is typically made incidentally based on clinical features and X-ray findings (8). The characteristic abnormality in PD is a metaphyseal remodeling defect, leading to widening of the metaphyses of long bones and cortical thinning, predominantly affecting the distal end of the femur and the proximal end of the tibia. Additionally, involvement may extend to the two-thirds proximal of the humerus and the two-thirds distal of the radius and ulna (7). Most patients do not require treatment. However, in certain cases, orthopedic intervention may be necessary for genuvalgum and fractures (4).

The studied 8-year-old patient exhibited most clinical features of PD, including genuvalgum, scoliosis, and dental irregularities, and the radiographic characteristics, such as typical EFD in the long bones, and genetic tests confirmed the diagnosis. Another factor that was consistent with the diagnosis of PD is the autosomal recessive inheritance pattern of the disease, and the fact that both parents were consanguineous.

The pathophysiology of PD involves impairment in SFRP4, a critical receptor for metaphyseal bone modeling, and any mutation of it leads to bone fragility. (9). In the present case, with this mutation, the patient experienced a femoral fracture one month after starting walking due to a trivial fall.

Christodoulou et al. reported a case of PD in which increased thickness of the skull and calvarium resulted in the narrowing of the facial canal and subsequent facial nerve palsy (10). In the current case, the examination of the facial nerve and other cranial nerves was completely normal, except for the presence of horizontal nystagmus. This finding may warrant further evaluation in similar cases, as, until now, horizontal nystagmus has not been reported in PD cases. In the studied case, potential explanations for this symptom, such as involvement of the brainstem or cerebellum, have been ruled out due to the normal brain MRI.

Peripheral motor polyneuropathy has a wide variety of potential differential diagnoses in children, including inflammatory neuropathies such as Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy, toxic and metabolic neuropathies, hereditary neuropathies such as Charcot-Marie-Tooth disease, and neuropathies due to systemic illnesses like diabetes, kidney disease, or autoimmune disorders (11). In this case, possible etiologies were ruled out through a comprehensive assessment, including history, physical examination, and findings from the electrodiagnostic study. Thus, her underlying disease, Pyle disease, may explain the abnormal test results.

Another condition that could be considered as a differential diagnosis for this patient is neuromuscular junction disease (NMJD). However, the fact that sensory and motor nerve conduction studies are usually normal in NMJD makes this diagnosis less likely. Additionally, within the context of NMJD, a myogenic pattern in the EMG is typically expected. Conversely, in the studied patient, a pronounced neurogenic pattern was found in all assessed muscles, as one would expect in motor neuropathy, with heightened severity in the distal muscles. Long-term follow-up is crucial for patients with PD to monitor disease progression and potential neurological complications. Since neuropathy has not previously been described in the literature as a feature of PD, this finding should be interpreted with caution, as it may not be representative of all patients with the condition. This underscores the need for further research to explore and understand this aspect more thoroughly and to determine whether these findings apply to the broader PD patient population (12).

In Conclusion

Although it is quite uncommon; nonetheless, it is crucial to remember that in the course of electrodiagnostic evaluations, when the obtained results suggest peripheral motor polyneuropathy defined by a mixed axonal and demyelinating type with a more pronounced impact on the lower extremities, and despite lacking a clear explanation for this, an evaluation of the patient's overall appearance, in conjunction with any accessible radiological characteristics, can assist in the diagnosis of PD.

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Authors' Contributions

Maryam Behroozinia: Conceptualization, Data curation, Methodology, writing – original draft, writing – review & editing.

Saeid Khosrawi: Conceptualization, Project administration, Supervision, Writing – review & editing.

Conflicts of interest

The authors have no conflict of interest to declare.

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