Case report

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A 23-Year -Female WithBoth Huller-Scheie Syndrome (Mucopolysaccharidosis Type I) And Hereditary Spastic Paraplegias 7: A Case Report

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1. Abstract

1.1. Background: Huller-Scheie syndrome, one of the phenotypes of mucopolysaccharidosis type I (MPS I), is a rare autosomal recessive lysosomal storage disorder, resulting in progressive deterioration. Hereditary spastic paraplegia (HSP), alternatively referred to as Strümpell-Lorrain disease, is a collection of neurodegenerative inherited neurological disorders that exhibit significant genetic and clinical heterogeneity. These disorders are caused by retrograde axonal degeneration of the corticospinal tracts.Spastic paraplegia 7 (SPG7) is one of the most common forms of autosomal recessive hereditary spastic paraplegia (ARHSP) caused by mutations in the SPG7 gene. In this report, we present the special case of a young female patient who may have both Hurler-Scheie syndrome (mucopolysaccharidosis type I) and hereditary spastic paraplegia7.

1.2. Case Presentation: A 23-year-woman presented with intermittent fever and abnormal mental behavior that had lasted for 10 days. The brain magnetic resonance imaging (MRI) revealed multiple abnormal signals surrounding the centers of the bilateral semiovale and the lateral ventricles, as well as punctate hyperintensities in the left parietal lobe.Genetic investigation for the female patient was conducted, revealing the presence of compound heterozygous SPG7 mutations (c.1150_1150-1insCTAC and c.1193G : A, p.Arg398Gln) as well as compound heterozygous IDUA mutations (c.1037T : G, p.Leu346Arg and c.236C ; T, p.Ala79Val), which were inherited from her mother and father respectively.

1.3. Conclusions: To the best of our knowledge, we are reporting a unique case in the Chinese population of a woman affected by both Hurler-Scheie syndrome and SPG7. Our findings have enhanced the understanding of spastic paraplegia in the context of mucopolysaccharidosis type I. Conducting research on this rare disease is crucial for enhancing diagnostic precision and patient outcomes.

2. Keywords: Mucopolysaccharidosis type I, Huller-Scheie syndrome, Hereditary spastic paraplegias

3. Background

Mucopolysaccharidosis type I (MPS I) is a rare inherited autosomal recessive lysosomal disorder caused by a defective alpha-L-iduronidase (IDUA) gene, an enzyme crucial for the degradation of glycosaminoglycans (GAGs or mucopolysaccharides). These mutations will lead to the buildup of dermatan sulfate and heparan sulfate in multiple tissues, resulting in progressive deterioration [1,2]. This condition is further classified into three subtypes: Hurler syndrome (MPS I H), Hurler-Scheie syndrome (MPS I H-S), and Scheie syndrome (MPS I S) [3]. The Hurler syndrome represents the prototypical type, being the most prevalent and severe manifestation of the condition. Specifically, patients develop symptoms shortly after birth and progress rapidly. The clinical symptoms encompass delayed development, cognitive decline, characteristic coarse facial features, joint stiffness and contractures, short stature, as well as cardiac and hepatic disease [4,5]. Hereditary spastic paraplegias (HSP) are a group of neurodegenerative and inherited heterogeneous neurological disorders

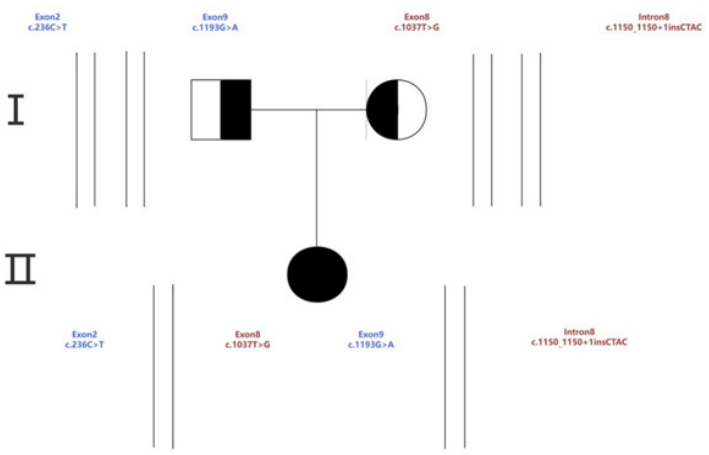
Annals of Clinical and Medical Case Reports

characterized by retrograde axonal degeneration of the corticospinal tracts. Specifically, hereditary spastic paraplegia 7 (SPG7) is one of the subtypes of autosomal-recessive hereditary spastic paraplegia (ARHSP) [6,7,16]. The clinical manifestations of SPG7 exhibit significant diversity, encompassing simple spastic paraplegia, spastic ataxia, hearing impairment, lower limb stiffness, gait instability, scissoring gait, dysarthria, and dysphagia.In addition, some patients will also exhibit symptoms resembling Parkinson's disease, bladder dysfunction, cognitive impairment, mood disorders, and epilepsy. Optic atrophy and retinal deformation may also manifest. Furthermore, other potential presentations include ichthyosis, extrapyramidal features, sensorineural hearing loss, peripheral neuropathy, and scoliosis.[8,9,10].In this study, we initially presented the clinical characteristics of a young female patient who is affected by both Hurler-Scheie syndrome and spastic paraplegia 7.

4. Case Presentation

A 23-year- female patient, whose parents are healthy and non-related and without similar family symptoms, initially exhibited symptoms including visual disturbances, facial dysmorphism, inguinal hernia, skeletal malformations, gait ataxia, and recurrent retrograde falls from the age of 19 years. After several rounds of therapy, the patient did not experience any relief from her symptoms. At the age of 23, her symptoms worsened after exposure to cold, and she also experienced intermittent fever, abnormal mental behavior, hallucinations, auditory hallucinations, irritability, emotional instability, poor sense of security, apathy, persecutory delusions, and aggressive behavior. It is noteworthy that she had not consumed any antipsychotic medications prior to her admission. Consequently, she was admitted to the neurology department of the General Hospital of Ningxia Medical University. The neurologic examinations revealed rough facial features, involuntary tremor of both eyelids, short neck, short stature, claw-like hands, clubfoot, and abdominal distension. The Spinocerebellar Ataxia Rating Scale (SARA) score showed 24 points (gait: 3.0, stance: 3.0, sitting: 0, speech: 4.0, finger chase: 4.0, nose-finger test: 4.0, rapid alternating movements: 2.0, heel-shin test: 4.0). Unfortunately, the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and Cerebellar Cognitive Affective Syndrome (CCAS/Schmahmann's) scale could not be completed. The patient exhibits left eye exotropia and uncorrected right eye esotropia; bilateral pupils unclear; no nystagmus. Sensory system examinations were normal; normal muscle strength in all limbs; increased muscle tone in all limbs; atrophy in bilateral lower legs and upper arms; broad-based gait; severe ataxia.

The right bilateral biceps brachii, triceps brachii, and radioperiosteal reflexes exhibited positive responses, along with the tendon reflex and ankle clonus on the right side. The right Babinski test was positive, but mostly normal on the left, with occasional urinary. Brain MRI demonstrated diffuse high signal intensity in the periventricular white matter (T2-FLAIR) (Figure 3). No abnormalities were detected in the video EEG monitoring. Ophthalmologic examination revealed corneal opacity and poor visualization of the fundus(Figure 4). The spinal MRI enhancement suggested a straightened cervical lordosis. Additionally, there was hemivertebra deformity at the level of T2; and no other unremarkable anomalies. Radiographs of the joints revealed bilateral irregularities of the shape of the radial and ulnar bone, and flexion deformities of the metacarpophalangeal joints. Both feet displayed eversion, flexion deformities of multiple toe bones, and multiple joint dislocations (Figure 5). Echocardiography and abdominal ultrasound were unremarkable. Auxiliary examination showed α-L-IDUA is decreased, with no abnormalities found in cerebrospinal fluid, thyroid function, rheumatology panel, immunoglobulins, anti-gliadin antibodies, folic acid, vitamin B12, adrenocorticotropic hormone, serum copper, ceruloplasmin, syphilis, HIV, and tumor markers. The binocular VEP visual conduction pathway is normal. Electromyography did not suggest myogenic or neurogenic injury. According to the clinical characteristics of the patient, it is considered that the condition may be related to hereditary diseases, so it is recommended to enhance genetic screening testing. After obtaining written informed consent from the patient and family members, as well as approval from the Ethics Committee of Ningxia Medical University General Hospital (Approval Number: KYLL-2024-0968), a venous blood sample was collected from the patient and sent to Ningxia Jinyu Medical Laboratory for further analysis. We employed fragment analysis techniques to capture and sequence target regions of genes associated with hereditary leukoencephalopathy and leukodystrophy-related disorders in the participant's genomic DNA, revealing the presence of compound heterozygous variations in the patient's IDUA gene, specifically c.1037T>G (p.Leu346Arg) and c.236C>T (p.Ala79Val). In addition, compound heterozygous variations were also identified in the SPG7 gene, with c.1150_1150+1insCTAC (p.Gly384Alafs*) and c.1193G>A (p.Arg398Gln) detected. Suspected pathogenic variations were confirmed in the proband and their family members using Sanger sequencing. Family verification results indicated that these variations were inherited from the parents. The mother carried c.1037T>G (p.Leu346Arg) and c.1150_1150+1insCTAC (p.Gly384Alafs*), while the father carried c.236C>T (p.Ala79Val) and c.1193G>A (p.Arg398Gln). The parents of the patient carried compound heterozygous mutations, which were clinically asymptomatic and consistent with the pattern of autosomal recessive inheritance (Figure 1, 2).



Annals of Clinical and Medical Case Reports

Fig. 1: Genetic results of family. Pedigree and the gene mutations of the Chinese family. The proband is indicated by a black solid diagram. #2A IDUAc.1037T>G (p.Leu346Arg)

According to the standards of the American College of Medical Genetics and Genomics (ACMG), p.Leu346Argand p.Gly384Alafs*can be classified as pathogenic, whereas p.Ala79Val and p.Arg398Gln are categorized as having uncertain clinical significance.All of the mentioned variants above are known types of variant categories.

Fig. 2: A. The upper diagram represents the plaintiff, while the lower diagram represents the defendants. The mutation sites are indicated by red arrows. Sanger DNA sequencing chromatogram demonstrating the heterozygosity for the c.1037T>G variant in the proband and his mother.B. Sanger DNA sequencing chromatogram demonstrating the heterozygosity for the c.236C>T variant in the proband and his father. C. Sanger DNA sequencing chromatogram demonstrating the heterozygosity for the c.1150_1150+1insCTAC variant in the proband and his mother.D. Sanger DNA sequencing chromatogram demonstrating the heterozygosity for the c.1193G>A variant in the proband and his father.

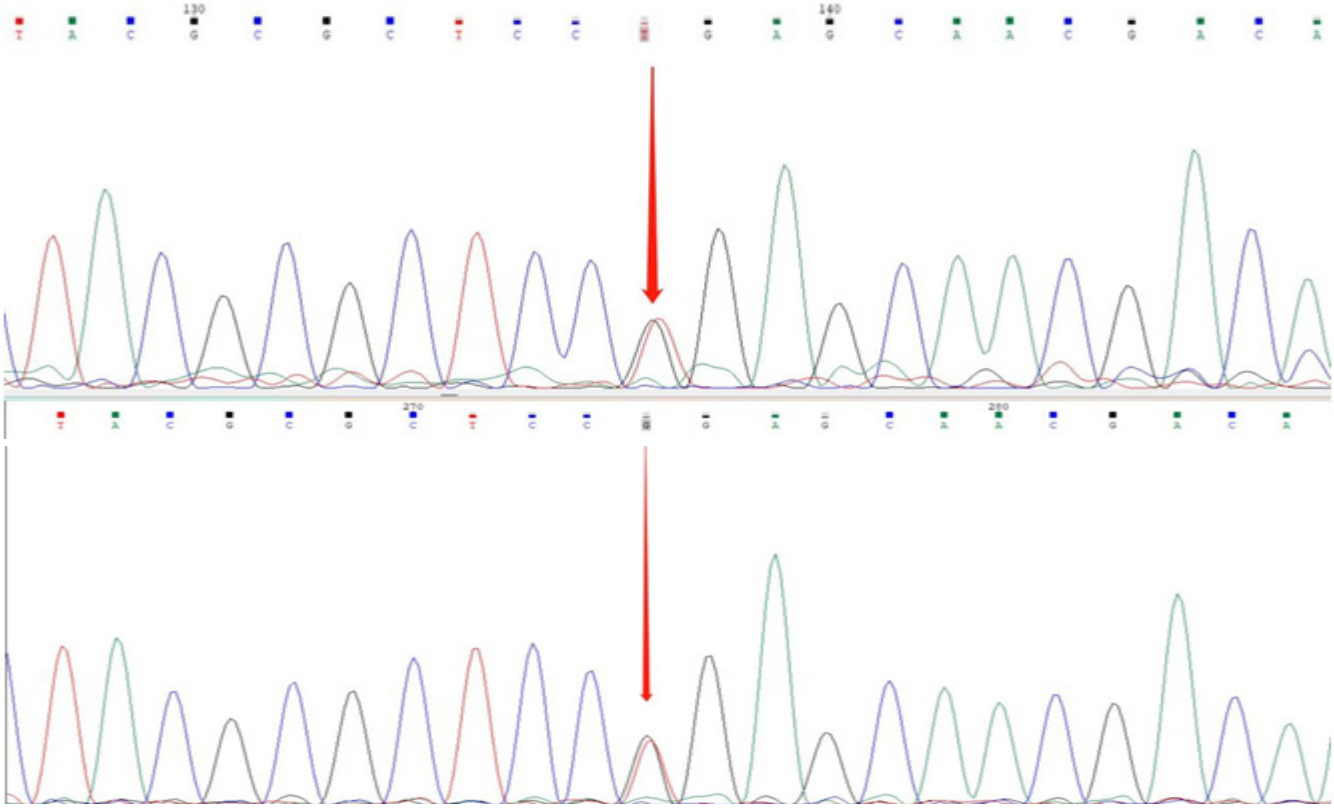
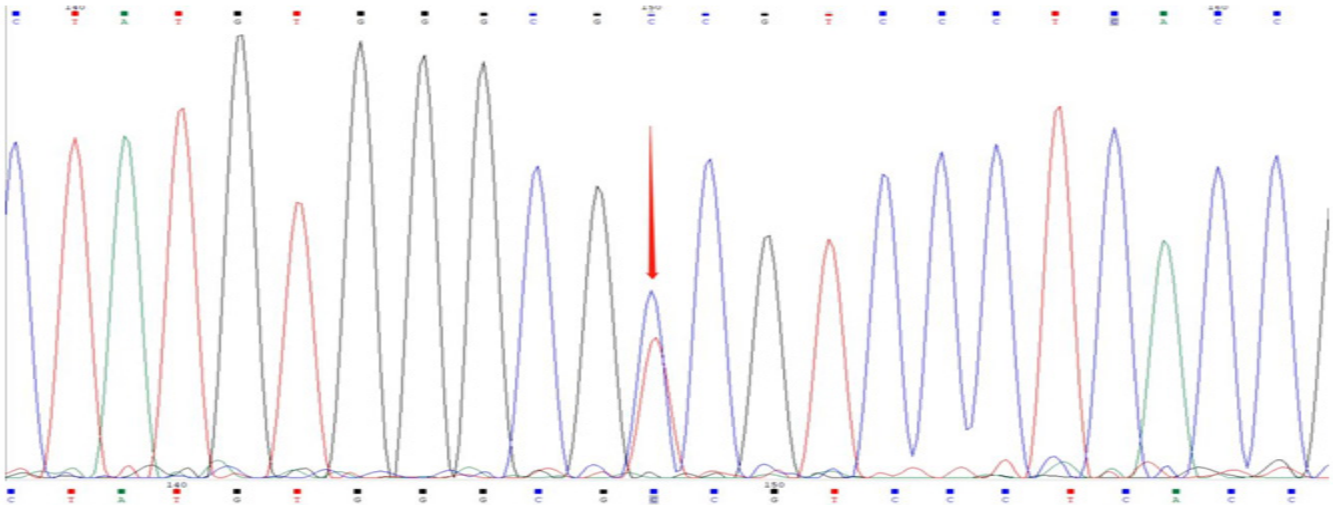


Fig 2B: IDUAc.236C>T (p.Ala79Val)



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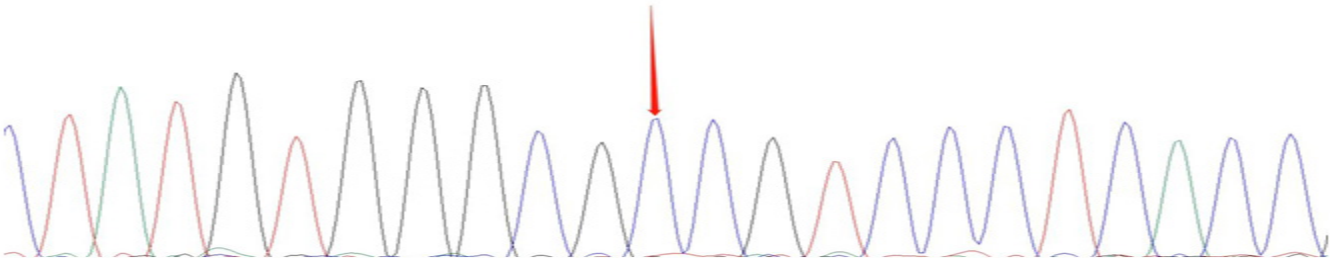

Fig 2C: SPG7c.1150_1150+1insCTAC (p.Gly384Alafs*)

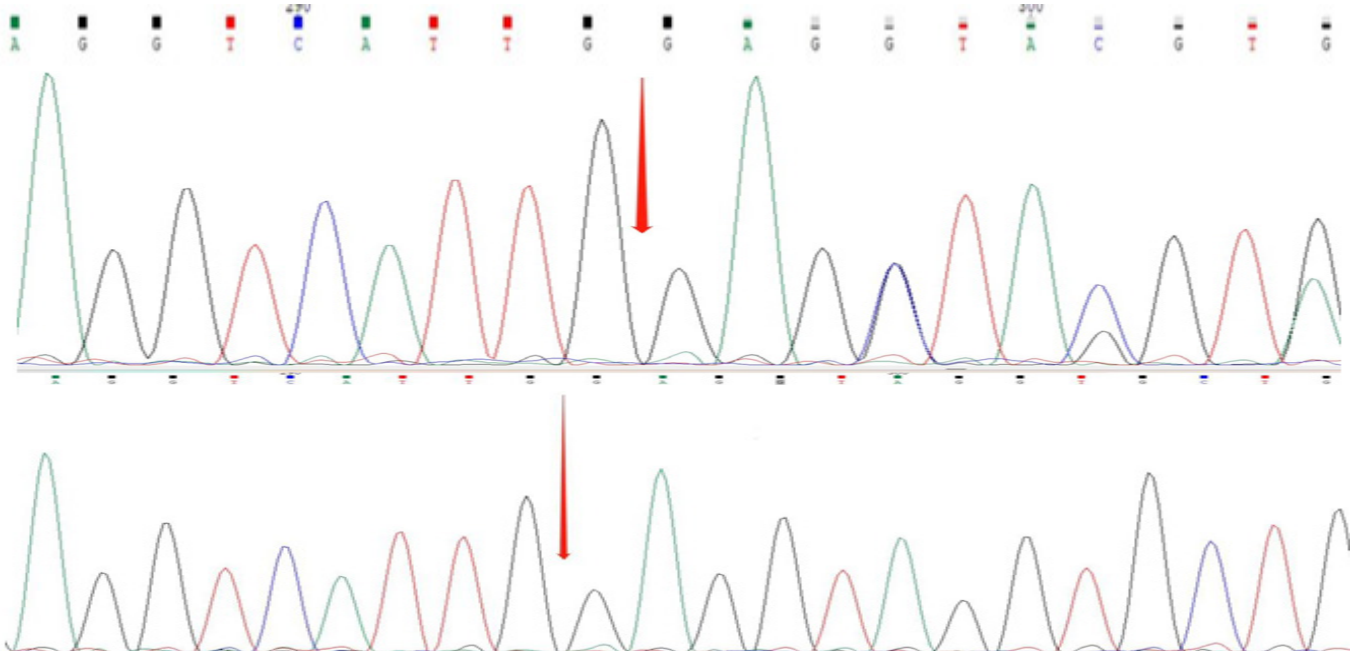

Fig 2D: SPG7c.1193G>A (p.Arg398Gln)

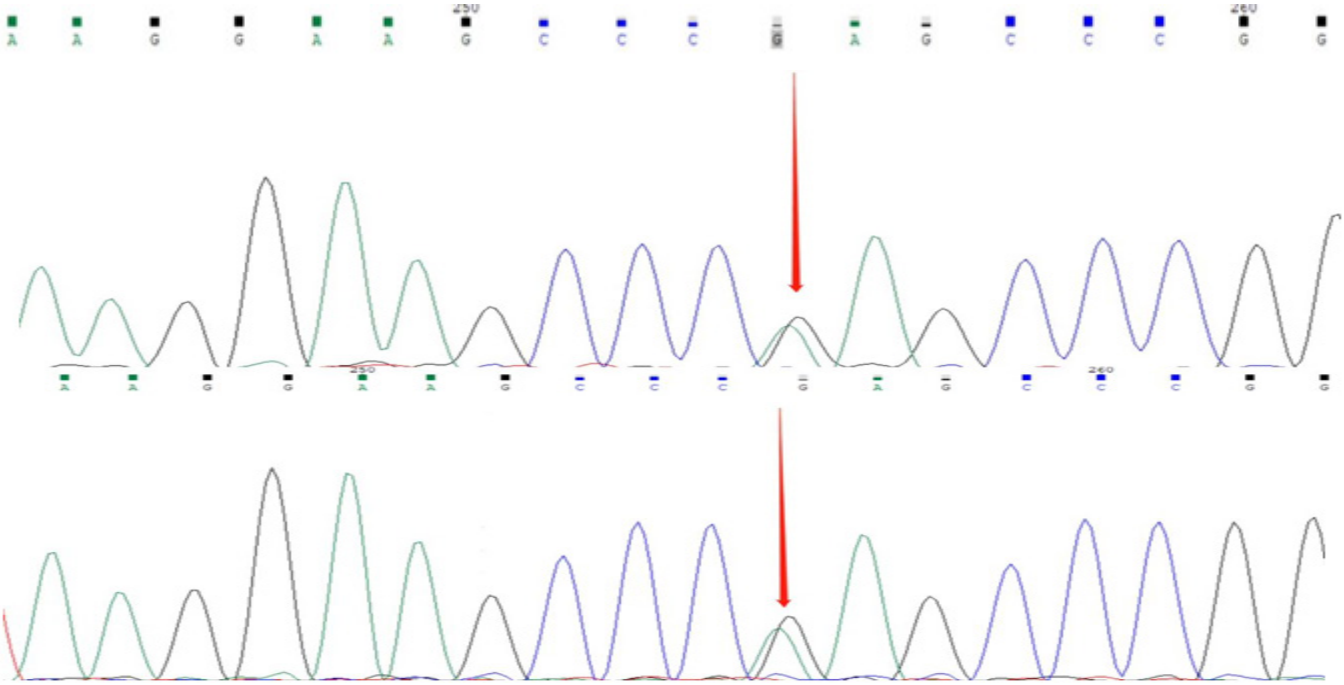

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Fig. 3: Brain MRI of a patient suggested diffuse high signal intensity in the periventricular white matter(T2-FLAIR).

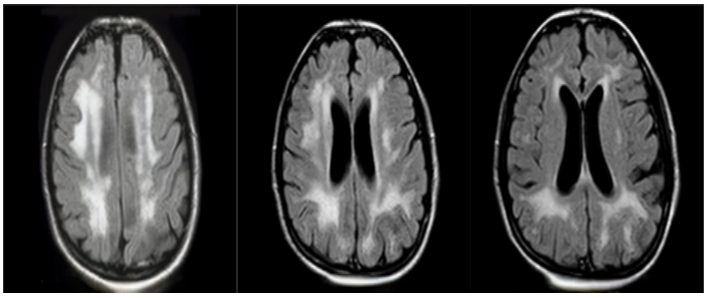


Fig. 4: Slit-lamp photographs of the anterior segment of the right eye (b) and the left eye (a) demonstrated cloudy corneas and a shallow anterior chamber. The patient was short-statured and had coarse facial features (c).

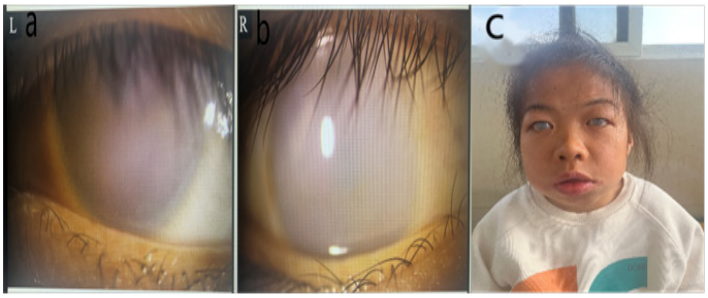
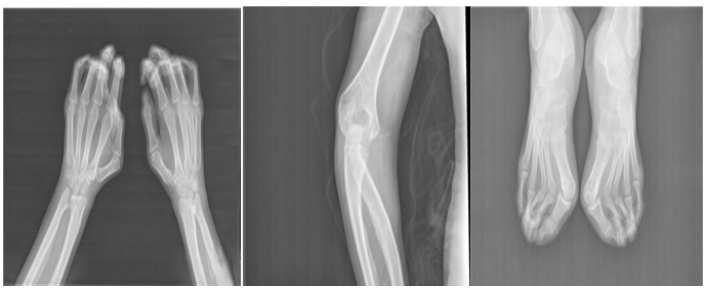


Fig. 5: The bilateral carpal bones display irregular shapes, and both fingers are flexed. The first metacarpal bone is short and thick. There is reduced density and localized cupping changes in the radiocarpal and distal radioulnar joint surfaces bilaterally. The right hand's first metacarpophalangeal joint is subluxated. There is bilateral elbow dislocation. Both feet are everted, multiple toe bones are flexed, and there are dislocations in the first metatarsophalangeal joint and third interphalangeal joint.



5. Discussion and Conclusions

Mucopolysaccharidosis type I is a progressive multisystem lysosomal disease, and its clinical phenotypes are associated with the IDUA genotype [11-13]. Clarke et al. [14]analyzed 530 cases of MPS1 patients, with the most common mutation in intermediate patients being missense mutations. In this study, the first reported individuals carry the IDUA gene with the missense mutations p.Ala79Val and p.Leu346 Arg, showing an intermediate phenotype consistent with previous reports. The HGMD database has currently cataloged over 300 mutations in the IDUA gene, with some mutations showing ethnic and geographic specificity. Edina et al. [15]found that p.Ala79Val and p.Leu346Arg were not identified in Western populations but reported more frequently in Chinese and Korean populations, being common mutations in Chinese patients. In the population of patients in Asia, p.Leu346Arg accounts for 23%, thereby reinforcing the view that the origin of the p.Leu346Arg allele lies in the East.

Through physical examination, we found that the patient also presented with ataxia, autonomic nervous function impairment, pyramidal tract involvement, extrapyramidal symptoms, psychomotor manifestations, and tremor symptoms. By reviewing the relevant literature, previous reports on IDUA disease could not be fully explained by mucopolysaccharidosis alone. Fortunately, we detected that the patient also harbors genetic variations in SPG7, with the variant sites being c.1150_1150+1ins CTAC (p.Gly384Alafs*) and c.1193G>A (p.Arg398Gln), compound heterozygous mutations. The patient underwent a comprehensive examination to rule out any other causes that may have induced her ataxia. For example, nutritional metabolic ataxia is one of the diseases we needed to consider. However, this disease is more common in groups of people with long-term alcohol abuse or vitamin B12 deficiency, which is not consistent with the actual symptoms of our patient. The patient's cranial MRI and tumor markers ruled out cerebrovascular disease and primary or metastatic tumors of the cerebellum. Furthermore, both serum and cerebrospinal fluid immunological tests were negative; therefore, demyelinating disorders are not currently being considered. In addition, we distinguished dopa-responsive dystonia, a condition whose symptoms typically present intermittently with diurnal fluctuations, which does not align with the clinical manifestations of our patient. Based on all of the above factors, we diagnosed the patient with probable Hurler-Scheie syndrome (mucopolysaccharidosis type I) and hereditary spastic paraplegia 7 simultaneously. The patient was finally diagnosed by genetic analysis.

SPG7 mutations are a potentially underrecognized cause of spasticity, ataxia, and other neurologic syndromes [19]. The c.1150_1150-1insCTAC mutation identified in this study is located in the highly conserved domain of paraplegin (AAA-domain; Peptidase M41 domain) [20]. These mutations are predicted to result in a truncated or defective protein involved in the degeneration of corticospinal tract and spinocerebellar Purkinje neurons, which could lead to progressive spasticity, weakness in the lower limbs, and ataxia [21]. HSP with persecutory delusions is a rare presentation. In 2022, Izadora [22] and colleagues first described a 23-year-old Caucasian SPG7 patient with mental illness, which attracted attention to the role of the cerebellum in cognitive and psychiatric disorders. The patient reported in theliterature exhibited symptoms such as apathy, persecutory delusions, aggressive behavior, and other psychological behaviors, which are part of the complex phenotype. She had no early manifestations of cognitive

impairment, psychosis, or trauma during adolescence. It can be explained that SPG7 is highly expressed in the Purkinje cells of the cerebellum. When the Purkinje cell density of the cerebellum is decreased, leading to impairment of cerebellum integration, the cerebellar-thalamic-cortical-cerebellar (CTCC) circuits are disrupted, resulting in delusions [7]. However, primary psychosis cannot be completely ruled out, and it is necessary to continue follow-up to observe the development of the patient's symptoms.

However, we concede that there is a valid possibility thatour cases represent acombination of manifestations associated with mucopolysaccharidosis, cerebellarataxia, corticospinal tract involvement, extrapyramidal symptoms, and psychiatric manifestations, rather than distinct diseases, namely SPG7 and MPS I H-S. Future research should continue to investigate this rare disease, emphasizing the relationship between gene mutation combinations and clinical phenotypes.In summary, this case is notable for its unique presentation of mucopolysaccharidosis and spastic paraparesis, linked to both IDUA and SPG7 mutations. The diagnostic challenges encountered herein may assist in the evaluation and management of similar cases, enhancing our understanding of both MPS and SPG7. Furthermore, we contribute to the body of observations regarding SPG7 within the context of MPS.Finally, our case report posits that the co-occurrence of an SPG7 mutation with an MPS-associated mutation could modify the clinical picture, potentially leading to an earlier onset or more pronounced presentation than would occur with either mutation alone.

6. Abbreviations

ACMG: American College of Medical Genetics and Genomics;ARHSP: Autosomal recessive hereditary spastic paraplegia; MRI: Magneticresonance imaging; SPG7: Spastic paraplegia 7; MPS I: Mucopolysaccharidosis type I; IDUA: alpha-L-iduronidase; MPS I H-S:Hurler-Scheie syndrome

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Publication Ethics

The ethics were approved by the General Hospital of NingxiaMedical University Research Ethics Committee [KYLL-2024-0968]

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