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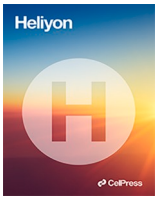

Case report

Intracranial tumor in a patient with mucopolysaccharidosis type 1 (Scheie syndrome): An extremely rare combination

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ABSTRACT

Scheie syndrome is a mild variant of mucopolysaccharidosis type I (MPS I), a rare group of lysosomal storage diseases that affect multiple organ systems. It is rarely associated with neoplasia. To the best of our knowledge, only a single case of mucopolysaccharidosis associated with a brain tumor has been reported, and it was nearly three decades ago. We present the case of a 10-year-old female with Scheie syndrome associated with a brain tumor. Physical and laboratory findings were suggestive of Scheie syndrome. A skeletal survey also revealed a spectrum of dysostosis multiplex supporting MPS. Children with MPS can have rapidly enlarging head sizes due to hydrocephalus, but our patient had several red flags that demanded further evaluation. A brain MRI revealed a mass in the fourth ventricle and a biopsy of the mass revealed pilocytic astrocytoma grade 1. Intraventricular pilocytic astrocytoma itself is a rare occurrence, accounting for only 4%–15.6 % of all pilocytic astrocytomas. Altered mucopolysaccharide metabolism can be involved in tumor pathogenesis, but the exact mechanism is unknown. Mucopolysaccharidoses, being a group of complicated disorders, are difficult to manage, and many symptoms can be missed in children due to intellectual disability. This case highlights the importance of suspecting brain tumors in children with mucopolysaccharidoses who present with signs and symptoms of increased intracranial pressure. Prompt diagnosis and management can save the child from dire neurological consequences.

1. Introduction

Mucopolysaccharidosis type I (MPS I) is one of the subtypes of mucopolysaccharidosis disorders. Lack of alpha-L-iduronidase, an enzyme responsible for the breakdown of glycosaminoglycans (GAGs) in lysosomes, causes a buildup of glycosaminoglycans [1]. A buildup of dermatan sulfate and heparan sulfate occurs in the body without this enzyme. Depending on the amount of functional enzyme produced, MPS I can cause a wide range of symptoms. MPS I is an autosomal recessive disorder. Patients with MPS I have two faulty copies of the IDUA gene on chromosome 4 [2], one from each parent. Based on the severity of symptoms, MPS I is divided into

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three subgroups. The enzyme alpha-L-iduronidase is absent or present in inadequate amounts in all three kinds. Hurler syndrome, also known as MPS IH, is the most severe of the MPS I subtypes; MPS IS (Scheie syndrome) and MPS IH-S (Hurler-Scheie syndrome) are the other two kinds.

Scheie syndrome is the mildest form of MPS type I and has similar signs and symptoms as severely affected children, but they have a slower disease progression and onset of symptoms at a later stage. A fundamental distinction between severe and milder variants is that patients with Scheie syndrome do not exhibit early developmental delays or a persistent decline in mental ability.

Children with Scheie syndrome usually have normal intelligence, although some children and young adults may have learning difficulties. During their adolescent years, they may develop hepatomegaly, heart valve problems, obstructive lung disease [3], developmental retardation, hearing loss, skeletal deformities [4], joint stiffness, or corneal clouding, which can cause serious issues with vision. Scheie syndrome has rarely been associated with tumor development. A search of the literature revealed only one case of intracranial tumor 'ependymoma' arising in a 19-month-old female child with MPS I [5]. Increased frequency of meningiomas has been reported in iduronidase-deficient cats [6]. A case of a teenager with concomitant Morquio's syndrome (MPS type IV) and osteosarcoma has also been reported [7]. The mechanism is unclear but altered mucopolysaccharide metabolism can be involved in tumor development [8]. We report a rare case of intraventricular pilocytic astrocytoma arising in a 10-year-old female child with MPS I. Roughly 4 %–15.6 % of all pilocytic astrocytomas are intraventricular, making them a rare occurrence [9]. This case report adheres to the CARE 2013 Guidelines [10].

2. Presentation

A 10-year-old female child presented with complaints of frequent falls and regression of milestones for the past one and a half years, blurred vision for five months and seizures for three months. There was no association of blackouts, abnormal posture, or any abnormal movement with these complaints. At first, the child could get herself up soon after falling, but gradually she stopped walking, and after a few days, she lost the ability to even sit. After that, her vision started deteriorating. She would search for objects placed directly in front of her. Abnormal eye movements were also observed by the parents, but hearing and speech were intact. For the last three months, she had developed generalized tonic-clonic seizures, which lasted for 10–15 minutes. She would lose control over her bladder and roll her eyes upwards during the seizures, but no postictal state, abnormal hand movements, or loss of lingual skills were observed. Her memory remained intact, and she could recognize family members. There was no change in behavior like aggression or throwing tantrums.

According to the mother, the child sometimes complained of headaches, especially in the morning, on the frontal aspect that used to last for an hour, often relieved by taking Ibuprofen. She had also complained of vomiting, which was projectile, but had no specific time. Her mother noticed that her head size was bigger than normal since birth, but her head size had been increasing abnormally fast for the past month. She was the third product of a consanguineous marriage. Her mother had three miscarriages and her three living siblings were healthy.

Upon examination, the patient's body weight was 23 kg (2nd percentile), height was 120 cm (<1 percentile), and frontal-occipital circumference was 53 cm (73rd percentile). She had coarse facial features, a flat nasal bridge, prominent bilateral temporal horns, an abnormal contour of the head, a large head size, and decreased visual acuity of both eyes with to-and-fro movement but without corneal clouding. She had a prominent chest, a short neck, and short and broad hands, but no scoliosis or kypho-scoliosis. On neurological examination, the child had mid-dilated non-accommodating pupils, power in the upper limbs was graded as 4/5 and in the lower limbs as 3/5, reflexes and tone were normal but had bilaterally upgoing plantar reflexes, and the test for clonus was negative.

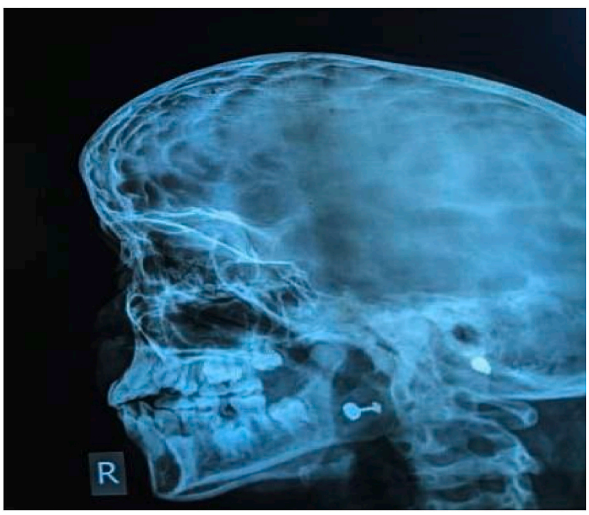

Fig. 1. Copper-beaten caused by gyral impressions on the inner skull, possibly due to raised intracranial pressure caused by the tumor.

She could not bear her weight on her legs, but sensations were intact in both upper and lower limbs. All other systemic examinations were unremarkable. Laboratory investigations revealed normal complete blood counts, which exclude infection as a cause of seizures, and electrolyte levels were normal as well.

A skeletal survey was done, which revealed mildly reduced bone density. Prominent convolutional markings representing a copper-beaten skull (Fig. 1) and a few wormian bones were seen in the lambdoid suture. The chest radiograph showed a widening of the anterior aspect of the ribs, with tapered posterior ends representing oar/paddle-shaped ribs (Fig. 2). Both lung fields appeared clear, and the cardiac apex was seen on the left side. Radiographs of the abdomen and spine were normal. Pelvic X-ray demonstrated widely flared both iliac bones with inferior tapering, poorly developed acetabular cavities with broad margins, coxa vara (angle between femoral head and shaft $<120^{\circ}$) on the right side, smaller and medially displaced bilateral femoral capital epiphysis but normal bilateral femoroacetabular articulation (Fig. 3). Extremity x-ray showed multifocal epiphyseal and metaphyseal irregularities and widening of all long and short bones of the hands. Both radii appeared shorter in length than the ulna, with oblique angulation of the distal part representing Madelung deformity (Fig. 4). Bullet-shaped short bones of hands and feet with the minimal proximal pointing of metacarpals and metatarsals, predominantly the 4th metacarpal, were found (Fig. 5).

These imaging appearances were suggestive of two possible diagnoses: mucopolysaccharidosis and multiple epiphyseal and metaphyseal dysplasia. To clinch the diagnosis, serum and urine glycosaminoglycans (GAGs) were checked, which came back positive

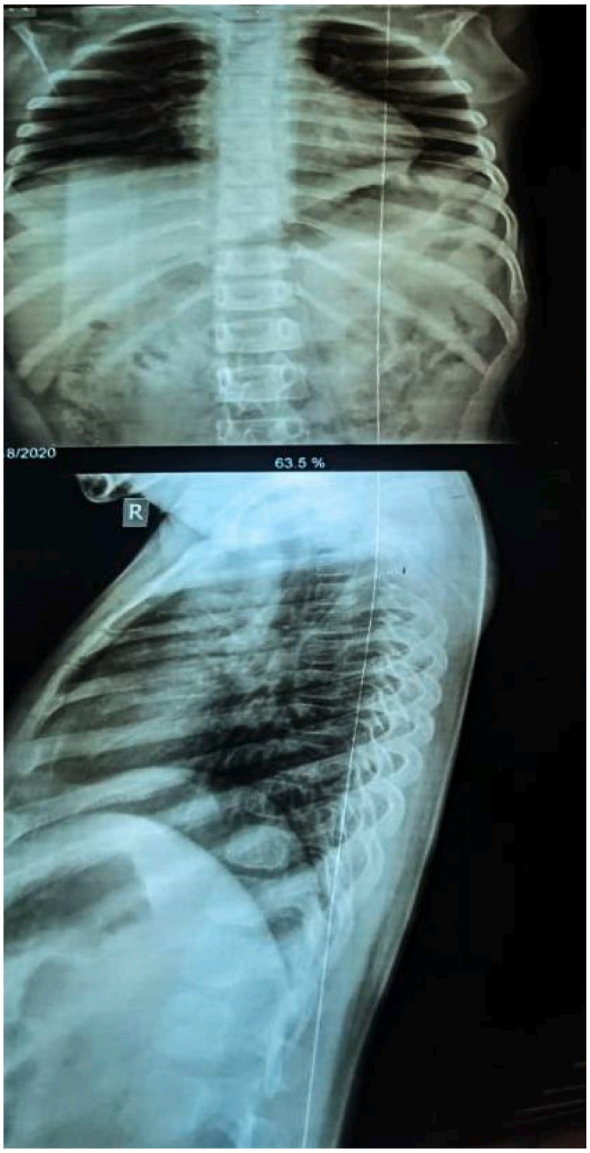

Fig. 2. Frontal and lateral projections of chest x-ray revealing widening of anterior ribs with tapered posterior ends representing oar/paddle shaped ribs.

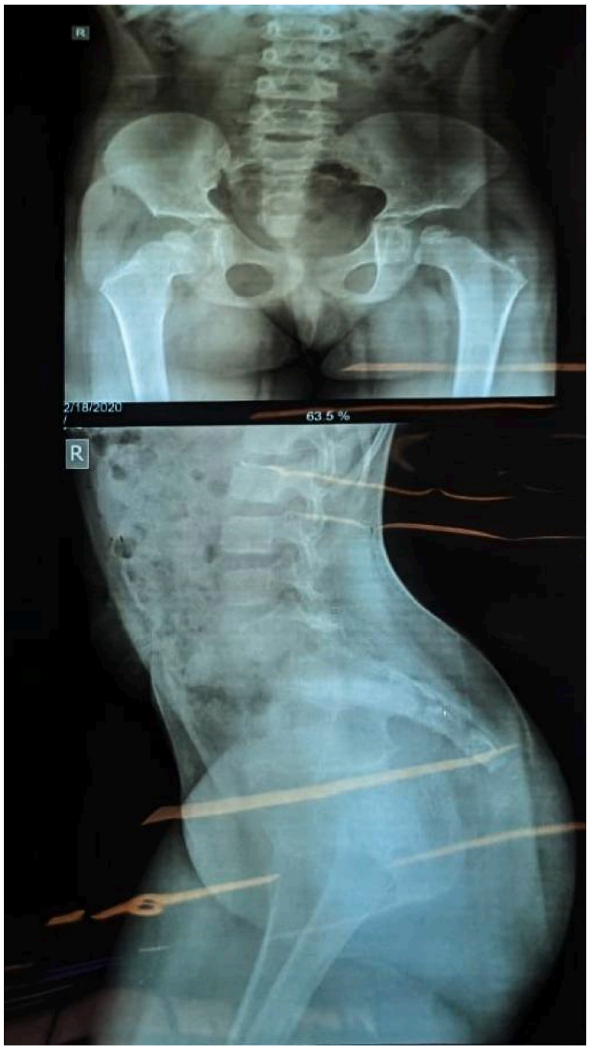

Fig. 3. Pelvic x-ray showing widely flared both iliac bones with inferior tapering and poorly developed acetabular cavities with broader margins. Both femoral capital epiphysis appear smaller in size and displaced medially. Coxa vara noted on the right side.

and confirmed the diagnosis of mucopolysaccharidosis. Enzyme assay showed decreased levels of alpha-L-iduronidase supporting MPS 1.

The patient was further investigated for impaired vision and increasing head size; the differentials for these findings were a space-occupying lesion, leukodystrophies, and neuromyelitis optica. Fundoscopic examination revealed bilateral papilledema and dull macular reflexes. The MRI brain with contrast showed a large, well-circumscribed, lobulated heterogeneous mass centered in the fourth ventricle (Fig. 6). It was mostly isointense to the adjacent cerebellum on the T1 weighted image (Fig. 7), hyperintense on T2 with areas of higher signal cystic change, and without significantly restricted diffusion (Fig. 8). Post-contrast images demonstrated vivid but heterogeneous contrast enhancement. It measured 4.0 x 4.2 $\times$ 5.0 cm in anteroposterior, transverse, and craniocaudal dimensions, respectively. The lesion obstructed CSF flow, resulting in severe supratentorial hydrocephalus. Focal vasogenic edema and a few abnormal vessels were also noted. The MRI of the spine was normal.

The patient was shifted to the neurosurgical department, and a ventriculoperitoneal shunt was placed the next day. After that, surgical excision of the posterior fossa mass was done. A biopsy revealed a neoplastic lesion showing bipolar cytoplasmic processes, Rosenthal fibers, and eosinophilic granular bodies with multiple dilated, hyalinized blood vessels. Microcytic change was also noted, along with foamy macrophages and calcifications. Features were consistent with pilocytic astrocytoma grade 1. The patient was discharged after a successful surgery. On follow-up, she is doing well now, and her head size is decreasing. She is also able to walk, but her vision is still impaired.

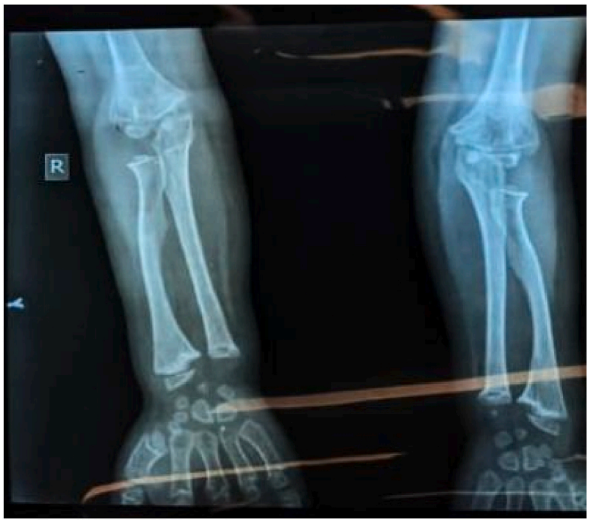

Fig. 4. Both radii are shorter in length in relation to ulna with oblique angulation of distal part (Madelung deformity).

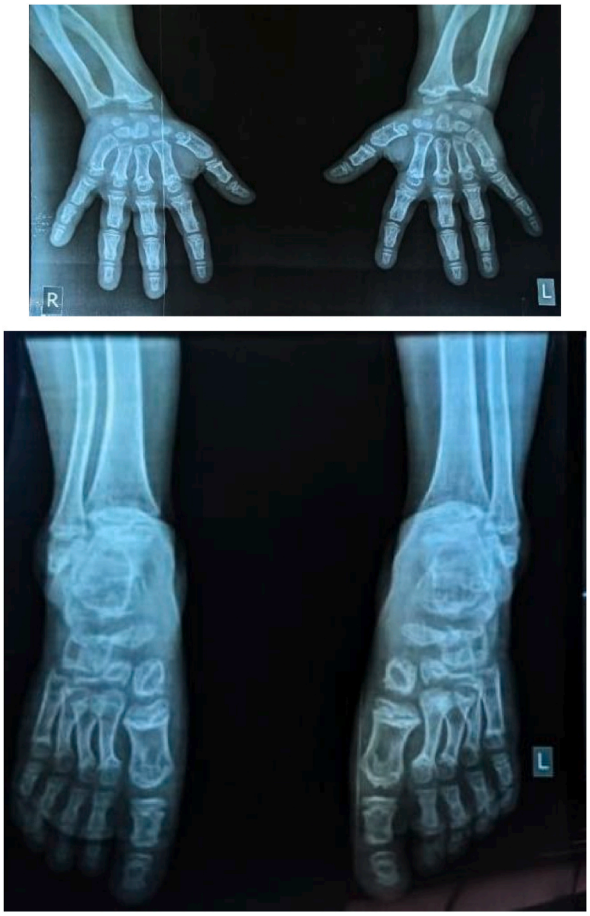

Fig. 5. Broad short bones of hands and feet with minimal proximal pointing of metacarpals and metatarsals predominantly 4th metacarpals.

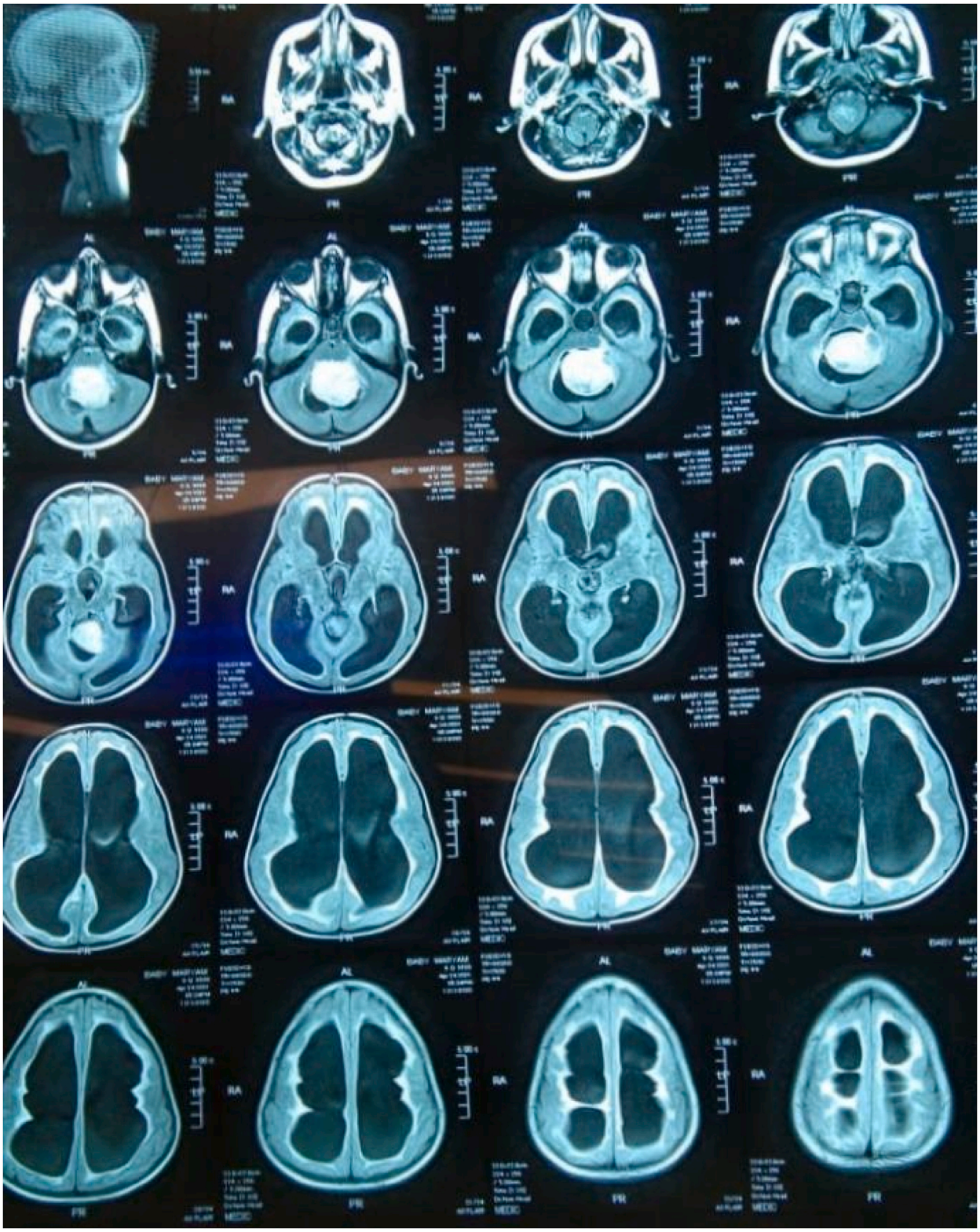

Fig. 6. MRI brain with contrast showing well-circumscribed lobulated heterogeneous mass in the fourth ventricle.

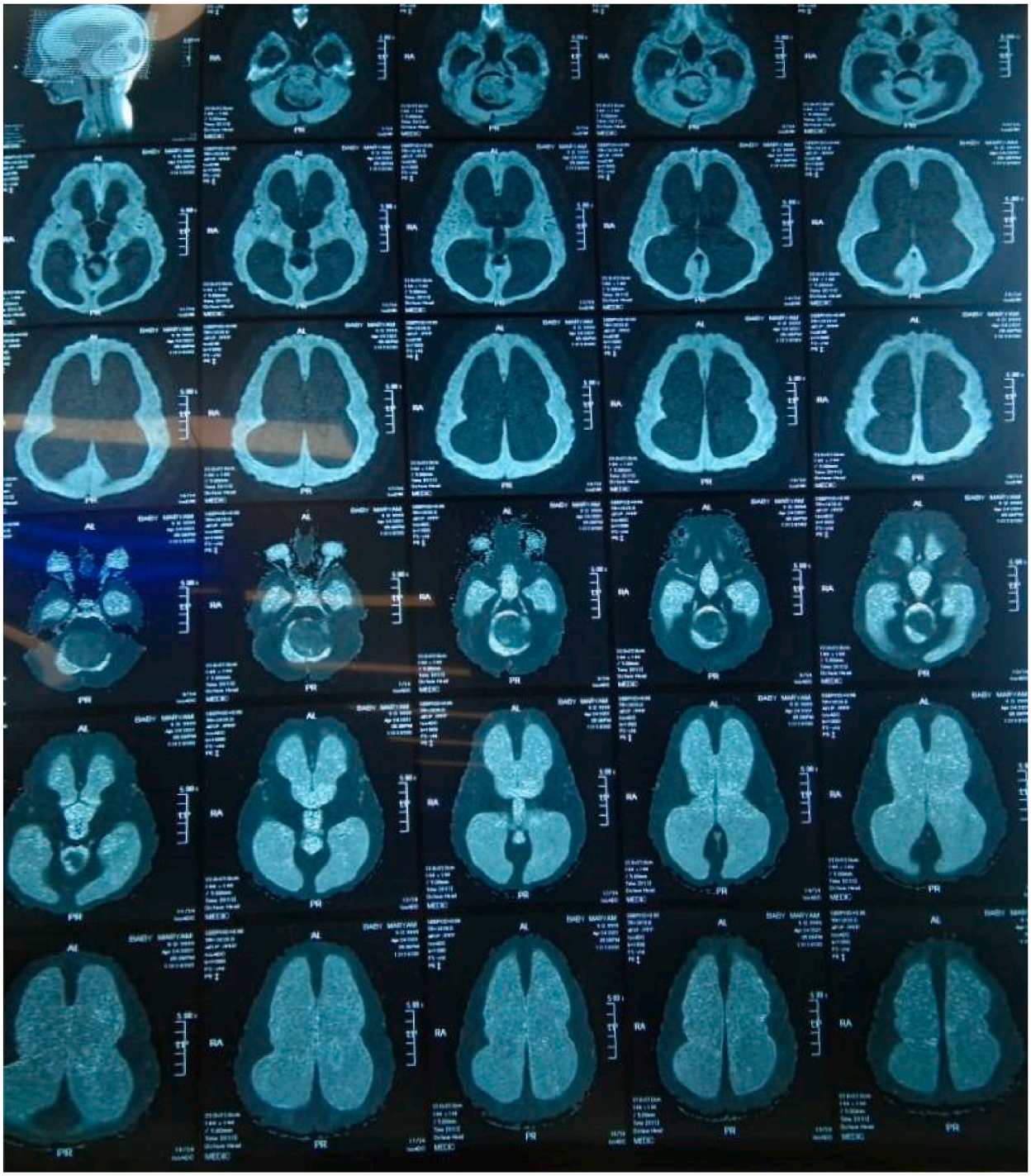

Fig. 7. T1 weighted MRI brain showing lesion isointense to the adjacent cerebellum.

3. Discussion

Lysosomes are membrane-enclosed organelles that contain a variety of enzymes that may degrade a wide range of biological polymers, including proteins, nucleic acids, carbohydrates, and lipids. Lysosomes serve as the cell's digestive system, degrading material taken in from outside the cell as well as digesting discarded components within the cell. About 50 distinct degradative enzymes can hydrolyze proteins, DNA, RNA, polysaccharides, and lipids in lysosomes. More than 70 different human genetic illnesses are caused by mutations in the genes that encode these enzymes, which are known as lysosomal storage diseases (LSDs) because

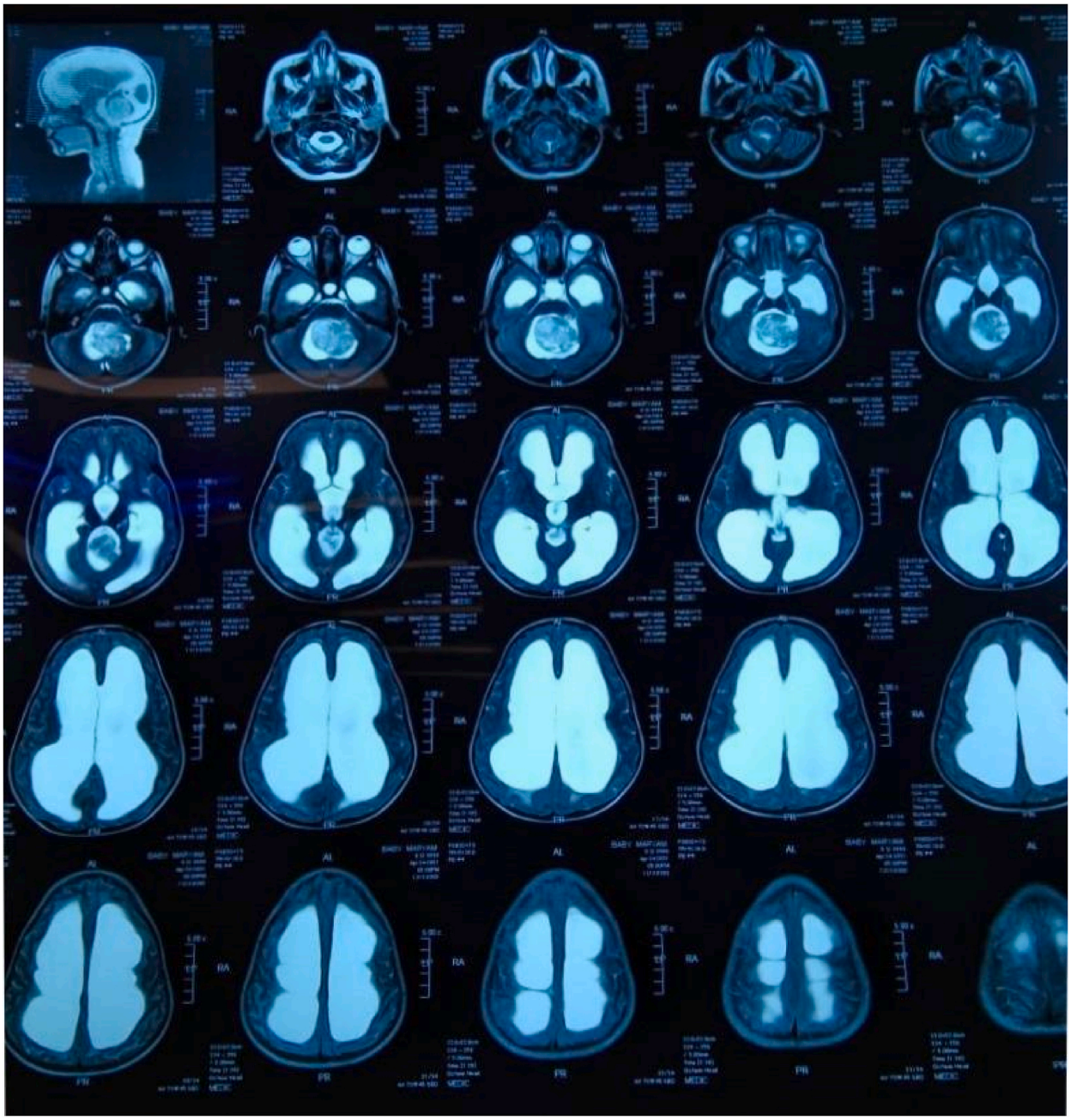

Fig. 8. T2 weighted MRI brain showing hyperintense lesion with areas of high signal cystic change.

undegraded material accumulates in the lysosomes of affected individuals [11].

MPS is a rare and heterogeneous group of lysosomal storage disorders characterized by a lack of catalytic enzymes that break down polysaccharides known as glycosaminoglycans (GAGs). GAGs are found in all connective tissue cells and are important in cell proliferation, cell surface binding, and histamine storage [12]. Twelve enzymatic deficiencies have been identified as being responsible for seven different forms of MPS (I, II, III, IV, VI, VII, IX and X) [13,14]. A defect in the activity of a particular lysosomal enzyme necessary for GAG degradation causes each MPS disorder [15]. Except for MPS II, which is an X-linked recessive illness, the majority of MPS is autosomal recessive [16]. Overall, one in every 25,000 births is affected by MPS, and the incidence varies depending on the type of MPS [17].

Within MPS types, GAG buildup in numerous tissues and organs results in a wide range of clinical symptoms and significant progression rates [18]. Hepatosplenomegaly, obstructive and restrictive pulmonary disease, heart valve disease, musculoskeletal abnormalities, decreased vision, and dental abnormalities are some of the somatic signs of MPS. MPS types I, II, IV, VI, and VII all have

these somatic symptoms [19]. Patients with MPS I, II, III, and VII experience neurological symptoms with clinical signs of aggressive, hyperactive behavior, developmental delay, cognition deterioration, epilepsy, hydrocephalus, and sleeping problems [20]. The radiological features of MPS, including macrocephaly, J-shaped sella turcica, thickened diploic space, oar/paddle-shaped ribs, short and thickened clavicles, gibbus, poorly developed acetabulum, inferior tapering of ilia, hypoplastic capital femoral epiphysis, long and narrow femoral neck, genu valgum, and bullet-shaped phalanges, are collectively referred to as dysostosis multiplex [21]. Diagnosis of MPS is usually done through clinical features as well as assessment of GAGs in urine and blood; in our case, these tests were relied upon for diagnosis. A confirmative diagnosis warrants an enzyme activity assay utilizing substrates specific for the enzyme lacking in each MPS type in leukocytes, fibroblasts, dried blood spots, or plasma, followed by additional clinical, molecular, and biochemical investigation [13].

Scheie syndrome is the mildest form of MPS I. The prevalence rate is predicted to be one in every 500,000 people. It is caused by mutations in the IDUA gene (4p16.3) and produces a partial deficit in the alpha-L-iduronidase enzyme and the lysosomal buildup of dermatan sulfate and heparan sulfate. Patients present with coarse facial features, a large mouth, and thick lips. Nasal secretion, sensorineural hearing loss, stiff joints, skeletal deformities, and carpal tunnel syndrome are all possible symptoms. Symptoms usually appear after the age of five, although they are so mild that diagnosis is often delayed until maturity. Patients are of nearly normal height and have no signs of mental illness. Corneal opacification develops gradually and diffusely after the age of four [22]. Lysosomes are important in the biology of cancer cells. Their effects can be carcinogenic or apoptotic, depending on the situation [23]. This is accomplished using cathepsins and other proteins in complex molecular pathways. It is considered that the extracellular release of proteolytically active cathepsins may promote angiogenesis, tumor development, and invasion. In terms of MPS associated with neoplasia, Gaucher disease, one of the lysosomal storage diseases, has been studied extensively. Patients with Gaucher disease have been diagnosed with carcinomas of the breast, prostate, colon, lung, ovary, kidney, bladder, liver, and thyroid; non-melanoma skin malignancies; ganglioneuroma; neurosarcoma; angiosarcoma; testicular rhabdomyosarcoma; carcinoid tumor, and hematological malignancies like multiple myeloma [24].

However, apart from Gaucher disease, lysosomal storage diseases in general, and MPS in particular, are rarely associated with cancer. This could be because patients with many MPS have a short lifespan.

In our case, the patient presents with rapidly increasing head size with likely MPS I variant Scheie syndrome, confirmed through clinical, physical, and laboratory findings. Intraventricular pilocytic astrocytoma was diagnosed through an MRI and biopsy of an intracranial lesion. Biopsy showed characteristic pilocytic astrocytoma grade 1 morphology in the background of mucoid material, indicating mucopolysaccharidosis. This shows that there might be a propensity for tumor development in MPS. The molecular mechanism of this relationship is unclear but abnormal mucopolysaccharide metabolism can be involved. It is still not confirmed if this relationship exists.

4. Conclusion

We conclude that lysosomal storage diseases in general and MPS in particular may be involved in the development of cancer. Our understanding of tumor development in the MPS type I variant is still unclear. We suggest that this mechanism should be investigated in greater detail and that further studies be done to confirm the nature of this relationship and whether it exists or not.

Although rare, intracranial tumors should be highly suspected in patients with MPS exhibiting signs and symptoms of hydrocephalus. If the intracranial tumor is removed at an early stage, permanent neurological damage can be avoided, and we can save a valuable life.

Ethical approval and consent to participate

Ethical approval is not applicable since we do not disclose any patients' information.

Consent for publication

Informed consent was obtained from the patient's parents to publish this case report and accompanying images.

Availability of data and materials

Not applicable.

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Code availability

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CRediT authorship contribution statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None to Declare.

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