TRANSIENT HYPERRENINEMIC HYPERTENSION AND THALAMIC INFARCTS IN AN INFANT WITH HURLER-SCHEIE SYNDROME

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Mucopolysaccharidosis (MPS) type IH/S is one of the lysosomal storage diseases that results from accumulation in the lysosome of glycosaminoglycans that would normally be degraded by hydrolytic enzymes present in lysosomes. The enzyme involved in MPS IH/S is α-L-iduronidase, and its deficiency leads to intracellular accumulation of partially degraded molecules that cause cell dysfunction and death. In contradistinction to other types of mucopolysaccharidoses, MPS IH/S is characterized by its slow progress and the occurrence of complications and death in the twenties or thirties. The mode of inheritance is autosomal recessive, and the disease affects the skeletal system, cardiovascular system, liver, spleen, tendons, joints and central nervous system, leading to physical and mental handicaps.

Case Report

A one-year-old Saudi girl presented with respiratory tract infection, for which she had been admitted to hospital repeatedly. She had a history of umbilical and anterior diaphragmatic hernia of Morgagni repaired at the age of eight months, followed by an incisional hernia. She was a product of consanguineous parents who had two other normal children. The perinatal period was uneventful.

Physical examination of the patient revealed normal weight, height and head circumference for age, scaphocephaly, coarse facial features that included thick supraorbital ridges, heavy eyebrows, wide-apart squinted eyes, hazy cornea, depressed nasal bridge, stuffy nose, thick lips, thick alveolar margins and spaced teeth. Midline scar and an incisional hernia were evident on the abdominal wall. Liver was 2 cm below the right costal margin and the spleen was just palpable. Genitalia were normal. There were extensive Mongolian blue spots on the lower back and no kyphosis. She had claw hands, genu valgum and delayed milestones. Using a modified Denver Developmental Chart, her intelligence and developmental quotients were just below 75%. There was bilateral eardrum bulge and type B tympanogram. The cardiovascular system was normal.

In view of these findings, investigations were carried out, including 24-hour urine mucopolysaccharides, the level of which was more than sixfold the normal value. Alder-Reilly bodies were not seen in the blood smear. Blood urea, electrolytes, complete blood count, fasting blood glucose and urine culture were normal.

Six months later, the patient was re-admitted with lethargy and refusal to feed that followed an attack of respiratory disease. Examination revealed a blood pressure of 220/160 mm Hg, with no appreciable difference or delay in the lower limbs. ECG showed left ventricular hypertrophy (LVH) and was confirmed by echocardiography, which showed dysfunction of both ventricles. Chest examination revealed impaired air entry in the left lower part posteriorly. Chest x-ray showed atelectasis of the left lower lobe, for which the patient received antibiotics and was maintained on physiotherapy.

Investigations for the possible causes of hypertension showed normal urinalysis. Serum sodium was 139 mmol/L, potassium 4.9 mmol/L, calcium 9.6 mg/dL, phosphate 5.2 mg/dL, BUN 7 mg/dL, creatinine 0.4 mg/dL, chloride 100 mmol/L, and there was a very high level of plasma

TABLE 1. *Laboratory investigations.*

Test	Result	Reference range
Urine:		
Mucopolysaccharides	1780 mg/g creat.	<262
Berry test	Negative	
TLC for oligosaccharides	Abnormal	
Free neuraminic acid	Negative	
α–L–iduronidase	1% of normal	
VMA	0.5 µmol/24 hour	<12
Cortisol	282.1 nmol/L	198-690
Noradrenaline	200 ng/L	<450
Adrenaline	281 ng/L	<125
Dopamine	20 ng/L	<85
Renin	2200 µU/mL	5-70
Renin: Drugs off	665 µU/mL	5-70
Aldosterone (serum)	27 ng/dL	5-60

TLC=thin-layer chromatography; VMA=vanillylmandelic acid.

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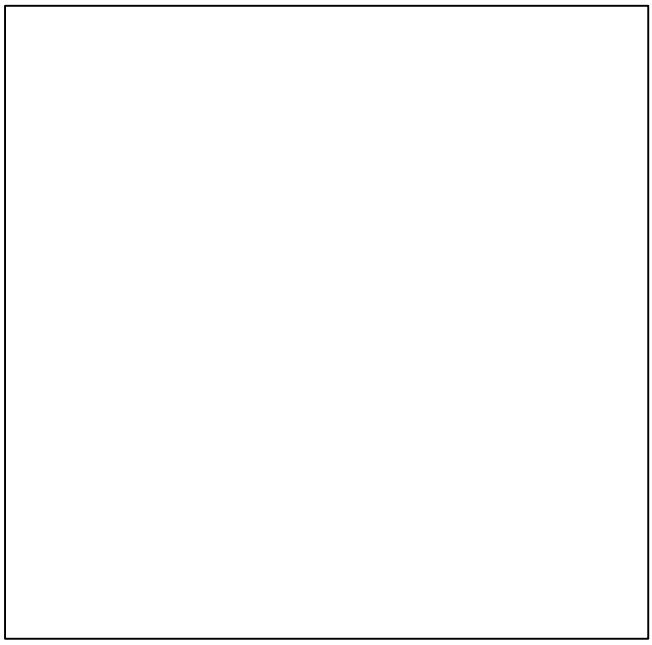

FIGURE 1. Axial CT scan of the brain showing a left lacunar thalamic infarct.

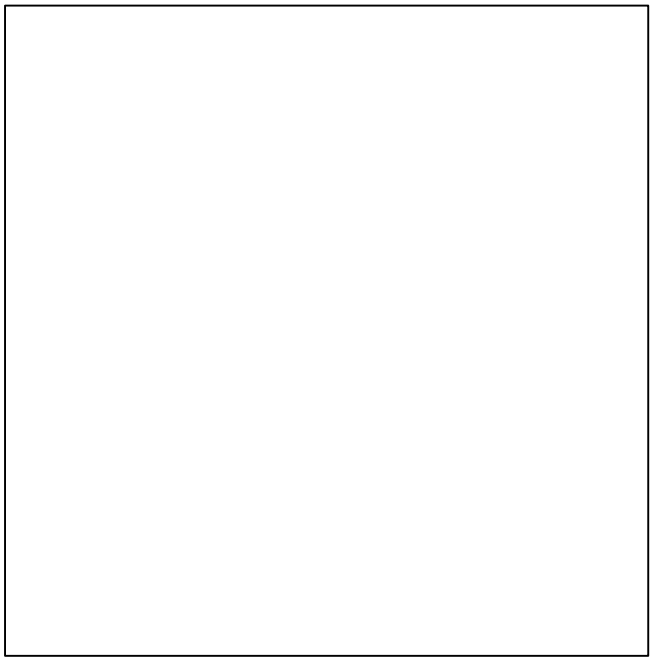

FIGURE 2. MRI of the sagittal section of the dorso-lumbar spine showing antero-inferior beaking of L_2 and L_3 vertebral bodies and expansion of the lumbar thecal sac. No kyphosis is seen.

renin (Table 1). X-ray of the skull showed enlarged sella turcica, and a brain CT scan showed left thalamic lacunar infarct and dilatation of ventricles (Figure 1). MRI of the abdomen and spine showed an incisional hernia, hepatosplenomegaly and beaking of L_2 and L_3 without kyphosis (Figure 2). These findings were not associated with gross neurological deficits. Vasodilators (hydralazine 1.8 mg/6 hrs), ACE inhibitors (enalapril 1 mg/12 hrs), and diuretics (frusemide 10 mg/8 hrs) controlled the blood pressure. Drugs were then tapered off and the patient continued to be normotensive, however, serum renin remained higher than normal (665 μU/mL). Consequently, the patient was referred to a tertiary hospital (KFSH&RC), where thorough investigations were done, including tissue fibroblast culture for α-L-iduronidase enzyme assay, and the diagnosis of mucopolysaccharidosis—Hurler/Scheie syndrome—was reached.

Discussion

Glycosaminoglycans (mucopolysaccharides) are macromolecules that form the intercellular matrix of hyaline cartilage and other connective tissues. Deficiency of specific enzymes responsible for their degradation is diagnosed by detection of the enzyme level in cells that contain lysosomes, e.g., leukocytes, skin fibroblasts and amniotic fluid cells. Partial degradation of these substances leads to excess excretion in urine of certain related metabolites. This provides further support to the clinical diagnosis, and helps to identify the type of the disease, which should be ascertained by enzyme assay.[1] Hunter described mucopolysaccharidoses as a group of diseases in 1917, but their biochemical basis was not established until the late 1960s.[2] Genetic studies showed that homozygosity or compound heterozygosity for W402X and Q70X mutations are the common causes of Hurler's severe form. The presence of R89Q may lead to milder phenotypes. However, the pattern of mutation has been found to be different in the Japanese, a fact that might point to a racial difference in these mutations.[3] Furthermore, the clinical picture of one and the same enzyme deficiency varies from mild to moderate and severe.

Hypertension in patients with mucopolysaccharidosis is reported to be common and sometimes severe.[4] In our patient, it was very severe, probably due to arteritis involving the renal arteries and a consequent renovascular disease, however, the role of increased intracranial pressure seen in this patient cannot be overemphasized. Renal angiography and an assay of renin in renal veins and the inferior vena cava would reveal the affected kidney. The heart is commonly involved in these patients, and thickening of the left ventricular wall, as seen in this patient, is well documented.[5] Wraith stated that in Hunter's type of mucopolysaccharidosis, even in mildly affected patients with normal intellect, brain CT scan shows cyst-like structures.[2] To our knowledge, this is the first report on lacunar thalamic infarcts in MPS IH/S. It is possible that these infarcts were due to hypoxic effects secondary to local arteritis. Another peculiarity pertaining to this patient was the presence of a diaphragmatic hernia, the repair of which led to a midline incisional hernia. Extensive Mongolian blue spots were seen in this patient, and this is

said to be due to disequilibrium of metabolism during embryonic development.[6] Enlarged sella turcica in these patients is often due to the presence of subarachnoid cysts,[7] however, cyst structures could not be demonstrated in our patient.

A wide spectrum of complications develops in these patients as they grow older, therefore, management needs a multidisciplinary approach. Of paramount importance in this age group is the nasal blockage that can lead to hearing defects and sinus disease.[8] Regular visits to the otolaryngologist are mandatory to prevent these complications. In cases that present for surgical procedures, it is important to be on the alert to the possible problems that may arise during anesthesia, e.g., difficult intubation, cardiac dysfunction and late awakening.[9,10] Spinal cord compression, joint stiffness and carpal tunnel syndrome are some of the late complications in these patients.[11] The orthopedic surgeon and the physiotherapist should be consulted for early management. Most of the patients with IH/S syndrome are educable and their future careers should be dictated by their mental and physical capabilities. An earlier age at diagnosis is likely to lead to a better result.[12]

Recent trends of management include early bone marrow transplant, which can reverse upper airway obstruction and intracranial hypertension,[13] though the post-bone marrow transplant course may be complicated by interstitial pneumonitis and hypertension.[14] Furthermore, bone marrow transplant does not prevent the hip dislocation that develops later.[15] Recombinant α-L-iduronidase enzyme replacement therapy is under trial. The presence of such an enzyme may lead to decrease in lysosomal storage of glycosaminoglycans and clinical improvement.[16] Neo-organ transplant is also under trial. Skin cells taken from infants soon after birth are genetically altered to incorporate a normal copy of the defective gene, grown in culture, and then reintroduced in infants so that they can produce the missing enzyme.[17] Genetic counseling and antenatal diagnosis remain the cornerstones of successful management and good prognosis.[18]

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