

10-year follow-up report and neurologic sequelae in a case of neonatal severe primary hyperparathyroidism

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Abstract

We present a 10-year follow-up and describe our experience in managing a case of neonatal severe primary hyperparathyroidism (NSHPT) for the first time in Iran. Microcephaly, mental retardation and epilepsy may be long time sequels of NSHPT and the brain MRI findings are compatible with old hypoxic-ischemic event.

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Key words: neonatal severe primary hyperparathyroidism, epilepsy, mental retardation, microcephaly.

Introduction

Neonatal severe primary hyperparathyroidism (NSHPT) is a rare, potentially life-threatening autosomal recessive disease characterized by severe hyperparathyroidism, marked hypercalcemia, and metabolic bone disease (1). Patients mainly present with poor feeding, failure to thrive, hypotonia, lethargy, polyuria, dehydration, respiratory distress, intestinal dysmotility, and skeletal demineralisation during the first few weeks after birth (2-6).

If not promptly diagnosed and treated, NSHPT can be associated with high mortality or irreversible neurodevelopmental, renal, skeletal, or cardiac complications (2). Although successful medical management of NSHPT has been recently reported (3,4), early parathyroidectomy followed by calcium supplementation and regular monitoring of serum calcium and PTH levels has been traditionally recommended as the definite therapy of NSHPT (2,5,6). However, neuromotor abnormalities may persist even after otherwise successful treatment of NSHPT patients, which warrants the long-term follow-up of these patients (1).

Considering the importance of long-term outcomes and prognosis of NSHPT, especially regarding neurological development and endocrine problems, we present a 10-year follow-up on a previously-reported case of NSHPT who underwent total parathyroidectomy on the 11th day of his life.

Case presentation

A 10-year-old boy, previously diagnosed with NSHPT, who underwent a total parathyroidectomy in our center on the 11th day of his life, was brought to our clinic for assessment of long-term outcomes. He was born full-term to consanguineous parents and delivered by cesarean section. He was admitted to our hospital on the 8th day of his life due to poor feeding and hypotonia and was diagnosed with NSHPT based on severe hypercalcemia (Ca=35mg/dl) and marked hyperparathyroidism (PTH=640 pmol/L.) and increased alongside with other findings consistent with NSHPT. As medical treatment (including intravenous normal saline, hydrocortisone, furosemide, calcitonin, and pamidronate) failed to stabilize serum calcium levels, the patient underwent total parathyroidectomy. The surgery was proved to be successful by a significant drop in serum calcium and PTH levels and the patient was started on calcium and vitamin D supplements a few days after surgery. Although the patient's NICU-stay was prolonged due to *Klebsiella* septic episodes treated with antibiotics and IVIG, he had normal calcium levels by the end of the fourth postoperative week while on calcium supplementation. . , His neonatal presentation has been described in detail elsewhere (7).

Following discharge from the hospital, the patient failed to attend follow-up visits until the age of 5 years, when he was admitted to another medical center due to new onset seizures and was started on antiepileptic medication. According to the patient's mother, seizures recurred at the age of 7 (electroencephalography (EEG) showing multiple epileptic discharges in a normal background) and Carbamazepine was prescribed. The patient experienced another recurrence at the age of 9 and is still on Carbamazepine. Moreover, he reportedly has had learning difficulties since school age and is currently attending a special school. According to his mother, the patient has had normal serum calcium and PTH levels on occasions when laboratory investigations were performed. Unfortunately, previous laboratory data are not available. At present, he is taking no calcium/vitamin D supplements. .

At the present visit, the patient's weight and height were 30kg (50th percentile) and 132cm (10th percentile), respectively, which is considered normal based on his age and his parents' weight and height. Patient's head circumference was 48cm (>2 standard deviations (SDs) below the mean for age and sex) which is consistent with microcephaly. The rest of his physical examination was insignificant. Additional investigations, including brain MRI, EEG, Wechsler Intelligence Scale for Children (WISC-IV), hand and wrist radiographs, and calcium, phosphorus and PTH serum levels, were performed.

. On EEG, multiple epileptic discharges in a normal background were observed, which is consistent with the previous EEG performed at the age of 7. Brain MRI revealed periventricular white matter volume loss with extension to the peri-rolandic region, which probably is a sequel of hypoxic-ischemic damage. Based on the results of WISC-IV, the full-scale IQ of the patient was calculated to be 54, which is consistent with mild intellectual disability. Patient's bone age was normal for his age based on hand and wrist radiographs. Laboratory investigations revealed normal serum calcium, phosphorus, and PTH levels.

Discussion and conclusion

Among hereditary causes of primary hyperparathyroidism, NSHPT is a highly uncommon autosomal recessive disorder, mostly caused by homozygous or compound heterozygous inactivating mutations in the gene encoding calcium sensing receptor (CaSR), a G-protein-coupled receptor expressed in the parathyroid glands, renal tubular cells, bones, and other organs, whose primary function is to maintain calcium homeostasis. Decreased sensitivity of the CaSR receptors to extracellular calcium results in PTH-hyperproduction and consequently, severe hypercalcemia (1), which can be potentially fatal or associated with severe neurodevelopmental impairments in untreated NSHPT patients (8, 9). On the other hand, early diagnosis and treatment of NSHPT usually leads to gradual improvement in growth and neurodevelopmental milestones (3,4,6).

Ten years after initial presentation, our patient has mild intellectual disability and microcephaly and is under treatment for epilepsy while according to his mother, he has had normal serum calcium and PTH levels on occasional laboratory tests performed during childhood. Although not common, neuromotor retardation may persist even in otherwise successfully-treated NSHPT patients (1), Savas-Erdeve et al. reported mild mental retardation in a 15-year-old girl with a history of NSHPT, in whom normocalcemia was maintained

by total parathyroidectomy, followed by calcitriol supplementation (10).

Our findings might be explained by exposure to severe hypercalcemia before parathyroidectomy, since hypercalcemia has been reported to induce cerebral vasoconstriction and subsequently, ischemia (11). At the present follow-up, the brain MRI findings were consistent with hypoxic-ischemic damage which may have been caused by the vasoconstriction induced by hypercalcemia during the neonatal period. Additionally, it has been hypothesized that CaSR plays a role in regulating the growth and development of the brain and inactivating mutations of CaSR may result in neurodevelopmental abnormalities (12).

Another explanation for hypoxic-ischemic damage in this patient is sepsis-associated encephalopathy. The pathophysiology of sepsis-associated encephalopathy is complex and multifactorial, including a number of intertwined mechanisms such as vascular damage, endothelial activation, breakdown of the blood brain barrier, altered brain signaling, brain inflammation, and apoptosis (13).

Based on these findings, we suggest that impairment of neurodevelopment caused by NSHPT may be multifactorial in nature. Therefore, we recommend a strict follow-up program for these patients in order to minimize the comorbidities and complications associated with the disease. Moreover, a pediatric neurologist should be involved in the management of these patients in order to facilitate early detection and reduce the neurologic complications that may arise. The major limitation of our study is the absence of genetic testing for the CaSR gene due to the high cost and difficulty of accessing this test in our country. To our knowledge, this is the first case report and the longest follow-up of NSHPT in Iran.

Authors Contributions:

Arya Afrooghe & Elham Ahmadi wrote 1st draft of manuscript.

Nahid Khosroshahi and Mahdiah Mousavi Torshizi wrote, reviewed and edited original manuscript.

Z. Haghshenas: Endocrine consultant

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Conflict of Interest

There is no conflict of interest to declare.

Ethical Approval

None.

Consent

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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