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Neonatal Severe Primary Hyperparathyroidism: A Case Report on the Successful Management of Hypercalcemia with Phosphorus Supplementation

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Abstract **Case Report**

Neonatal Severe Primary Hyperparathyroidism (NSHPT) is a rare autosomal recessive disorder caused by inactivating mutations in the calcium-sensing receptor (CaSR) gene, leading to severe hypercalcemia and elevated parathyroid hormone levels. We report the case of a 7-day-old girl who presented with hypercalcemic crisis and was treated with hyperhydration, bisphosphonates, and phosphorus supplementation. Despite initial management, cinacalcet showed limited efficacy, suggesting a homozygous phenotype. Long-term management remains challenging, with surgery being the ultimate solution. Genetic analysis is crucial to guide treatment strategies.

Keywords: Neonatal Severe Primary Hyperparathyroidism, Hypercalcemia, Phosphorus supplementation, Cinacalcet.

INTRODUCTION

Neonatal Severe Primary Hyperparathyroidism (NSHPT) is a rare life-threatening autosomal recessive disorder in which the calcium-sensing receptor (CaSR) is inactivated due to homozygous or compound heterozygous inactivating mutations in its gene, located on chromosome 3q21.1 [1]. The CaSR plays a key role in regulating the phosphocalcic metabolism through the control of the parathormone secretion and the urinary calcium excretion in response to variations in calcium plasma levels [2]. Subsequently, this inactivation elevates the calcium setpoint in plasma leading to hypersecretion of parathormone and hence, increased bone resorption and renal absorption of calcium [1].

Newborns affected with this disorder typically present with very high PTH levels and severe hypercalcemia [3]. The primary goal of medical management is to control calcium levels and prevent sequelae. For long-term treatment, some studies report successful and sufficient medical treatment using type II calcimimetic drugs, while others emphasize surgical intervention as the ultimate solution [4,5]. We report our experience managing a newborn girl from 7 days of life to 4 months of age in the neonatal unit at CHU Hassan II in Fez, Morocco.

CASE REPORT

A 7-day old girl was referred to our neonatology unit due to a poor muscle tone associated with refusal to feed. She was born by a primigravida woman by cesarean section delivery, from a 1st degree consanguineous marriage. At birth, she weighed 3000g.

On examination, she was dehydrated, lethargic and had a weight of 2600g, which prompted a biological evaluation. The latter revealed severe hypercalcemia at 323 mg/L, associated with a very high PTH level of 1877.9 pg/mL, vitamin D deficiency <3.5, hypophosphatemia at 10mg/l, all in favor of primary hyperparathyroidism.

After hyperhydration with bisphosphonates, loop diuretics administration and phosphorus supplementation, adjusted calcium attended 77 mg/L and normal values after 2 days which prompted her discharge on daily clinical and biological monitoring.

After 5 days, she was readmitted in a hypercalcaemia crisis with hypotonia and a 10% estimated dehydration. She was managed with hyperhydration, cinacalcet, furosemide, bisphosphonate, after which, calcium levels improved transiently. However, these levels rose again to attend 157 mg/L of calcaemia, just after the stop of furosemide despite continuing cinacalcet 10 mg/kg a day. Finally, we got the

calcemia stabilized between 90 and 110 mg/L with 4 mmol/kg a day of phosphorus supplementation.

Radiological investigations showed a normal cervical ultrasound, while the 99mTc-MIBI scintigraphy was indicative of a pathological parathyroid process in the lower left position. The cervical CT scan did not reveal any nodular lesion suggestive of a parathyroid adenoma.

Given this clinical and biological presentation, a genetic study is essential to confirm the etiology and guide future therapeutic decisions especially in the event of persistent resistance to medical treatment.

Our patient is a candidate for parathyroidectomy but the delay in surgery made us resort to long term phosphate therapy to stabilize calcemia levels while monitorin for side effects.

DISCUSSION

Neonatal Severe Primary Hyperparathyroidism (NSHPT) is a rare, inherited disorder, usually transmitted in an autosomal recessive manner, characterized by the inactivation of calcium-sensing receptors (CaSR). These receptors, normally present in the parathyroid glands and kidneys, are responsible for regulating calcium homeostasis in the body by responding to changes in plasma calcium levels. When inactivated, as in the case of NSHPT, this regulation is disrupted, leading to persistent hypercalcemia.

In newborns, this condition typically presents with symptoms such as nausea, failure to thrive, lethargy, and poor muscle tone. These signs are often accompanied by significantly elevated total calcium levels, which can range from 200 to 320 mg/L [6]. levels that are well above normal. In our case, the patient presented a hypercalcemic crisis as early as her first week of life with a calcium level of 323 mg/L, which corresponds to the typical levels observed in this condition. This phenomenon is particularly concerning due to the risk of serious complications, such as kidney and heart issues, if not promptly treated.

The treatment of acute hypercalcemia requires an aggressive approach to rapidly bring calcium levels into a safe range. In the literature, it is widely accepted that the management includes hyperhydration to promote renal calcium excretion, the administration of bisphosphonates to inhibit bone resorption, and loop diuretics (such as furosemide) that help reduce calcium levels by increasing urinary calcium excretion [7- 9]. These treatments allow for the rapid restoration of serum calcium levels and help prevent acute complications of hypercalcemia. However, it is important to note that while acute hypercalcemia can be controlled relatively quickly, maintaining optimal calcium levels over the long term is a more complex challenge. This requires close monitoring and careful dose adjustments to prevent a recurrence of hypercalcemia while minimizing potential side effects of the treatments [10].

Cinacalcet is an allosteric activator of CaSR, used to modulate the receptor's response to calcium and aid in the management of hyperparathyroidism, both acutely and chronically. Cinacalcet has shown variable efficacy in clinical studies, particularly for heterozygous forms of the disease. It is often used in cases where hypercalcemia is resistant to other treatments. However, in our case, cinacalcet did not effectively reduce symptomatic hypercalcemia, suggesting that the patient may have a homozygous phenotype [1,11,12]. Homozygotes, who have two copies of the defective gene, typically present a more severe form of the disease and may be less responsive to conventional treatments like cinacalcet. This observation emphasizes the importance of ongoing genetic studies to refine the diagnosis and adapt treatment accordingly. Genetic analysis would help better understand the underlying mechanisms and guide future therapeutic strategies.

In our case, phosphorus supplementation played a key role in normalizing calcium levels. We administered 4 mmol/kg of phosphorus per day, which helped stabilize calcium values to a safer range. Phosphorus is an important regulator of calcium metabolism, and its supplementation in this context works by reducing bone resorption, which in turn decreases blood calcium levels. However, it is important to highlight that the side effects of long-term phosphorus supplementation are not well understood, especially in cases where primary hyperparathyroidism is resistant to conventional treatment. Additionally, excessive phosphorus supplementation may lead to complications such as hyperphosphatemia, which can result in soft tissue calcifications, particularly in the kidneys and blood vessels.

Few studies have explored the long-term side effects of phosphorus supplementation, particularly in resistant cases of primary hyperparathyroidism. However, a study conducted in 1980 demonstrated the effectiveness of long-term phosphate therapy in treating hypercalcemia in rare cases of inoperable parathyroid carcinoma and cases of symptomatic disease where adequate neck and mediastinal exploration failed to locate the parathyroid adenoma [13]. This study supports the idea that, although managing severe primary hyperparathyroidism can be complex and requires a personalized approach, phosphorus supplementation remains a viable treatment, especially in cases where surgical interventions are contraindicated or ineffective. Therefore, it is essential to continue monitoring patients receiving long-term treatment to prevent complications associated with this therapy.

CONCLUSION

Neonatal Severe Primary Hyperparathyroidism is a rare genetic disorder resulting from the inactivation of the calcium-sensing receptor CaSR gene. This uncommon disease requires urgent management to tide over the subsequent lifethreatening hypercalcemia and prevent the eventual developmental delay. Long term treatment may involve the use of type II calcimimetic drugs whose effect depends of the remaining functionality of CaSR and/or oral phosphore supplementation with constant monitoring for the side effects. Surgical intervention is the ultimate solution in most cases.

Conflicts of Interest: The authors declare no conflicts of interest.

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