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Research Article

Surgical Management of Neonatal Severe Hyperparathyroidism

Saud Al-Shanafey, Sabreen Maqbol, Ali AlAmeer, Faiqa Ahmad and Abdullah Al-Ashwal*

Department of Pediatric Surgery, King Faisal Specialist Hospital and Research Center, Saudi Arabia

Abstract

Introduction: Neonatal Severe Hyperparathyroidism (NSHPT) is a rare disease that can be lethal. Most patients with it require parathyroidectomy. We report our experience in managing this severe disease at a tertiary healthcare center.

Materials and methods: A retrospective chart review was conducted for patients managed for NSHPT from June 2001 to January 2023. Demographic, clinical, and follow-up data were collected, and descriptive data were generated.

Results: NSHPT in 19 patients (13 males and 6 females), with a mean age of 46 days at referral, was managed with parathyroidectomy. The mean Preoperative Parathyroid Hormone (PTH) and serum calcium levels were 996 ng/L and 4.54 mmol/L, respectively. Twelve patients underwent ultrasonography preoperatively. Of these, six had prominent glands, while no glands were visualized in the other six. A Sestamibi scan was done for 15 patients, of which nine showed negative results and six showed positive results, with three glands observed in the neck and three in the sublingual area. Nineteen patients underwent renal ultrasonography, with nine showing nephrocalcinosis. The mean age at surgery was 5.2 months. Total parathyroidectomy (four glands) was performed in 17 patients, and 15 underwent concurrent auto-transplantation. One patient had three glands removed, in addition to auto-transplantation. Another underwent single gland excision as a redo-surgery after previous surgery elsewhere. The mean postoperative follow-up duration was 6 years. The mean postoperative PTH and calcium levels were 25 ng/L and 1.64 mmol/L, respectively. Ultimately, all the patients were required to initiate calcium and Vitamin-D supplements, except for two patients who had undergone auto-transplantation. Molecular genetic screening of the calcium-sensing receptor gene reported likely pathogenic/pathogenic mutations in 16 of 19 patients (13 were homozygous, two were heterozygous, one was negative, and data was unavailable for the remaining three patients).

Conclusions: Surgical treatment of NSHPT is effective. Preoperative radiological localization studies did not impact the treatment plan. Auto-transplantation proved ineffective in maintaining independence from medical supplements.

Keywords: Neonatal hyperparathyroidism; Hypercalcemia; Parathyroidectomy; Thyroid gland

Abbreviations

NSHPT: Neonatal Severe Hyperparathyroidism; PPH: Preoperative Parathyroid Hormone; FHH: Familial Hypocalciuric Hypercalcemia; US: Ultrasonography; *CASR*: Calcium-Sensing Receptor; PTH: Parathyroid Hormone

Introduction

Primary hyperparathyroidism is a common endocrine disorder that is characterized by hypercalcemia and elevated or inappropriately normal levels of the Parathyroid Hormone (PTH) [1]. It is sporadic in adult patients and is considered rare in the pediatric population, with an incidence of 2-5:100,000 and a higher rate of complications [2-5]. A minority of these cases have a genetic connection, including Familial Hypocalciuric Hypercalcemia (FHH) and Neonatal Severe Hyperparathyroidism (NSHPT).

Neonatal hyperparathyroidism disorders are relatively rare, and the NSHPT subcategory is infrequent [6,7]. Its onset is usually in the neonatal period and early infancy. Patients typically present with severe hypercalcemia that manifests as irritability, failure to thrive, hypotonia, constipation, polyuria, dehydration, osteopenia, and respiratory symptoms [7]. It is caused by a mutation in the Calcium-Sensing Receptor (*CASR*) gene, which leads to loss of function. *CASR* is distributed widely in the body tissues and can be found in the parathyroid glands, renal tubular cells, and parafollicular cells of the thyroid gland and bones [6].

We have previously reported our experience in managing five patients with NSHPT [8]. However, in this study, we gained a better insight by expanding our cohort significantly. We have also compared our findings with those of a case series reported recently.

Materials and Methods

We retrospectively reviewed the patients diagnosed with NSHPT who were managed at a tertiary healthcare institution from June 2001 to June 2021. Patients who presented with symptomatic hypercalcemia during the neonatal period (serum calcium level >2.6 mmol/L), a high PTH level (>65 ng/L), and low serum phosphate level (<1 mmol/L) were included in this study. Those patients with nephrocalcinosis on renal ultrasonography were also included.

Demographic and clinical data for patients who underwent surgical management for NSHPT were collected, and descriptive data were generated. These included gender, onset of disease, and age at diagnosis, age at the time of surgery, clinical presentation, laboratory and imaging studies, surgical procedures, pathology, post-surgical follow-up, and molecular results of *CASR* gene screening.

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***Corresponding author:** Saud Al-Shanafey, Department of Pediatric Surgery, King Faisal Specialist Hospital and Research Center, Takhassusi street, PO Box 3354, MBC-36, Riyadh 11211, Saudi Arabia, Tel: +966-555428080

Parathyroidectomy was performed *via* a low-collar cervical incision, and the glands were systematically searched for. All the patients underwent intraoperative histological confirmation of the excised parathyroid tissue. To confirm the adequacy of parathyroidectomy, the PTH level was initially measured 24 h after surgery and every 24 h thereafter till it stabilized. In the last six procedures, with the availability of a rapid PTH assay, the PTH level was measured intraoperatively 15 min-20 min after the excision of the last parathyroid gland, and a 50% drop in its level was considered satisfactory.

The clinical research and ethics committees approved this study at our institution's Research Affairs Committee (RAC #2231024). Given the retrospective nature of the study and its design, a consent waiver was obtained.

Results

A total of 19 patients (13 males and six females) with NSHPT who were managed surgically at our institution from June 2001 to June 2021 were included in this study. Their mean age at referral to our center was 46 days (Standard Deviation (SD): 23 days; range: 7-150 days) and they all developed NSHPT within 2 weeks of birth. The presenting symptoms in most of the patients were lethargy, poor feeding, and irritability. One patient presented late with vague abdominal pain, and renal ultrasonography revealed bilateral nephrocalcinosis. The mean PTH level at presentation was 996 ng/L (normal range: 15 ng/L-65 ng/L), and the mean calcium level was 4.54 mmol/L, (normal range: 2.1 mmol/L-2.6 mmol/L) (Table 1). The mean preoperative phosphate level was 0.79 mmol/L (normal range: 1 mmol/l-1.8 mmol/l), and the mean calcium/creatinine ratio was 0.04 (SD: 0.03). Initial medical management started with intravenous hydration and diuresis (Lasix) for all patients. In addition, 12 patients required calcitonin, five required hydrocortisone, and four required pamidronate. Cervical US were done for 12 patients (six tested positive for suspicious cervical lesions, while the other six were reported as normal). A Sestamibi scan was performed for 15 patients, and only six tested positive for parathyroid gland. Positive scans were not specific and detected a single gland (three cervical and three sublingual). Eighteen patients underwent renal US, and nephrocalcinosis was evident in nine of them. Two of the latter improved postoperatively on serial follow-up US, and the rest showed stable findings with maintained renal function. All 19 patients underwent total parathyroidectomy, and 15 of them underwent concurrent auto-transplantation (re-implantation in the forearm in five patients and in the sternocleidomastoid muscle in 10). One patient underwent sublingual exploration initially, based on the preoperative Sestamibi scan. However, we could not find any parathyroid tissue. One week later, a formal cervical exploration revealed four parathyroid glands. No thyroid or thymus resections were performed in our study. Three patients underwent redo-parathyroidectomy at our institution after an initial failed exploration elsewhere (one underwent the removal of one gland, one had three glands removed, and no glands were found in one). All of them underwent successful re-exploration, with the removal of the residual parathyroid glands. The mean age at surgery was 5.2 months (range: 3 weeks to 24 months). All the specimens revealed parathyroid hyperplasia. Postoperatively, all patients had hypocalcemia, with a mean calcium level of 1.6 mmol/L, which was managed with intravenous calcium infusion, oral calcium, and Vitamin-D supplements. The mean postoperative PTH and phosphate levels were 25 ng/L and 1.6 mmol/l, respectively (Table 1). No major surgical complications were encountered in any of our patients; specifically, there was no recurrent laryngeal nerve injury. The mean follow-up duration was 6 years (range: 8 months-17 years). Seventeen of 19 patients are still dependent on Vitamin-D and calcium supplementation and could not be weaned off. The remaining patients who underwent auto-transplantation (sternocleidomastoid muscle) were weaned-off medications a few months after surgery.

A retrospective review of the molecular genetic analysis of the coding regions of the *CASR* gene was available for 16 of the 19 patients. Likely pathogenic/pathogenic mutations were reported in 15 patients (13 homozygous and two heterozygous), and the remaining individuals were reported to have no variations in the *CASR* gene.

Discussion

Neonatal hyperparathyroidism is relatively rare and has a few forms that are associated with gene abnormalities. Genetic testing for this group of patients has evolved over the last 2 decades. In general, neonatal hyperparathyroidism occurs in the following four forms: autosomal recessive familial parathyroid hyperplasia [7,9], autosomal dominant FHH due to heterozygous mutations in the *CASR* gene [10], NSHPT with homozygous or compound heterozygous mutations in the *CASR* gene, and sporadic neonatal hyperparathyroidism with de novo heterogenous *CASR* mutations [11]. NSHPT is the rarest and most severe disorder, with serious morbidities and high mortality rates.

The *CASR* plays an important role in calcium homeostasis. It is a G-protein receptor encoded by chromosome 3p-13.3-21, expressed mainly in calciotropic tissues involved in calcium metabolism, such as the parathyroid glands and kidneys [6]. Inactivation of *CASR* (resulting from loss-of-function mutations) leads to hypercalcemia. Recently, it has also been found in non-calciotropic tissues, such as the pulmonary, vascular, and gastrointestinal tissues.

A mild form of hypercalcemia that is usually asymptomatic and has a familiar pattern, known as FHH, is believed to be caused by heterozygous loss-of-function mutations with variable phenotypes [6,10,12-14]. Some patients with FHH present with a severe form of hypercalcemia that may mimic NSHPT and pose a diagnostic and therapeutic dilemma, especially relative to the role of surgery [15]. Two of our patients had the severe form of FHH with heterozygous mutations and required parathyroidectomy.

Radiological imaging has been ineffective in localizing parathyroid hyperplasia in patients with NSHPT [8]. Cervical US, computerized tomography, magnetic resonance imaging, and nuclear scans (Sestamibi scan) have been utilized with variable success. Despite the recent enthusiasm for new imaging modalities, their applications in patients with NSHPT are limited, and our series attests this [16,17]. Moreover, false positive results may delay effective exploration and treatment. Due to a false positive result on Sestamibi scan, one of our patients had to undergo unnecessary sublingual exploration; subsequent neck exploration revealed the four glands in their native position.

Table 1: Preoperative and postoperative parameters.

Parameter	Preoperative	Postoperative
Mean serum calcium level in mmol/L (SD*)	4.54 (1.3)	1.6 (0.4)
Mean parathyroid hormone level in ng/L (SD)	996 (874)	25 (9)
Mean serum phosphate level in mmol/L (SD)	0.79 (0.2)	1.6 (0.3)

*SD: Standard Deviation

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Initial management of NSHPT involves aggressive hydration, diuresis, calcitonin, and the possible use of pamidronate as a single agent or in combination, to prevent hypercalcemia [18,19]. The latter improves bone mineral density and has a relatively long-lasting effect. The use of calcimimetics (e.g., cinacalcet) has also been introduced as a treatment option for these patients with some success [20]. It modifies the sensitivity of the *CASR* to the serum calcium level and decreases the proliferation of the parathyroid chief cells, and subsequently, PTH secretion [21]. Although some success has been reported with medical agents, it is generally unsustainable and recurrence has been reported. Mortality rates as high as 70% to 90% have been noted among patients with NSHPT with medical management alone, with long-term complications seen among survivors [22]. Recently, radiofrequency ablation of the parathyroid glands, performed by an experienced interventional radiologist under ultrasound guidance, has been successful in treating refractory hypocalciuric hypercalcemia caused by a novel inactivating mutation in *CASR* in an adult [23]. However, difficulty in localizing the parathyroid glands in patients with NSHPT may limit the utility of this option.

The ideal management of NSHPT involves urgent surgical removal of the parathyroid glands, with or without auto-transplantation [7,8,24]. This surgical approach is necessary to prevent the catastrophic complications of the disease and is thought to be cost-effective [25]. Our study, which is the largest single-center experience report, supports this approach. We strongly believe that due to the significant recurrence rate after subtotal parathyroidectomy, total removal of the parathyroid tissue should be the primary goal of surgical intervention [10,26,27]. Auto-transplantation in neonates has been adopted earlier, based on its success in adult patients [28,29]. Our success with parathyroid auto-transplantation is modest, as only two patients could be weaned off replacement therapy (calcium and Vitamin D). The retrospective nature of the study, variability in the auto-transplantation surgical technique, and the weaning-off of replacement therapy may explain this high failure rate. Additionally, there are limited outcome reports with a long follow-up in neonates after parathyroid auto-transplantation. We had three redo-parathyroidectomies in our study after failed total parathyroidectomy attempts at the referring centers (one patient underwent the removal of one gland only, one had three glands removed, and no glands could be found in one patient). This affirms the need for experienced pediatric surgeons for such procedures to avoid unnecessary failed explorations and to minimize complications.

The postoperative PTH level is used to document the complete removal of the parathyroid tissue to avoid persistence of the disease or relapse. The PTH level was routinely measured 24 h after surgery. In the last six cases, with the improvement in rapid assays, we were able to measure the PTH levels intraoperatively, 15 min-20 min after the excision of the last parathyroid gland.

In conclusion, parathyroidectomy remains the mainstay of treatment for NSHPT to avoid severe complications and high mortality. Preoperative imaging studies have a limited impact on NSHPT, and auto-transplantation has not been successful in our experience. Major strides have been made with the genetic characterization of conditions involving hyperparathyroidism, but its impact on the management of NSHPT has not been evident due to its severity and rarity. Genetic testing may be beneficial in borderline cases where FHH is suspected. Even in these cases, parathyroidectomy may still be needed to control the disease [30]. In future, genetic testing, especially prenatally, may have some utility in prevention, early recognition, and management.

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