Aetiology, Diagnosis and Surgical Treatment of Primary Hyperparathyroidism in Children: New Trends

Swethan Alagaratnam^{a, b} Tom R. Kurzawinski^{a, b}

^aCentre for Endocrine Surgery, University College London Hospital and ^bCentre for Endocrine Surgery, Great Ormond Street Hospital, London, UK

Key Words

Primary hyperparathyroidism · Familial hyperparathyroidism · Parathyroid surgery · Paediatric parathyroid surgery · Minimally invasive parathyroidectomy

Abstract

Primary hyperparathyroidism (PHPT) in children is a rare disorder with sharp contrasts in its presentation and aetiology compared with the disease process in adults. This review outlines the current literature, which is limited to about 200 cases, with reference to the aetiology, clinical features, outcomes of investigations, and surgery in children affected by PHPT. Familial conditions account for almost half of all cases of PHPT in children, suggesting that routine genetic testing would be appropriate. Neonatal severe hyperparathyroidism requires urgent medical attention, and performing total parathyroidectomies offers cure, though conservative management is successful in selected cases. Familial hyperparathyroidism in older children can be caused by conditions such as multiple endocrine neoplasia types 1 and 2a, hyperparathyroidism-jaw tumour syndrome and familial hyperparathyroidism. The role of surgery for this group is discussed. The use of ultrasound and MIBI (^{99m}Tc-methoxyisobutyl nitrate) scanning appears to accurately localise solitary adenomas in sporadic PHPT, thereby supporting the role of minimally invasive parathyroidectomy in children.

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Introduction

Primary hyperparathyroidism (PHPT) affects patients of all ages. In adults it is a common condition and much is known about its epidemiology, clinical course, accuracy of imaging, and outcomes of surgical treatment. In contrast, PHPT in children is very rare, and such information is sparse as only about 200 cases have been described in the world literature [1–9].

Surgical management of PHPT in adults has seen a sea of change in the last two decades. The main drivers for this change were faster and more sensitive biochemical assays, increased ability to detect genetic mutations and more accurate imaging of abnormal parathyroid glands. Clarity of biochemical and genetic diagnosis and better imaging allowed for the introduction of 'keyhole' parathyroid surgery. The majority of adult patients could now be selected for minimally invasive parathyroidectomy (MIP) and benefit from the surgery performed through smaller incisions, better scars, less pain, and reduced hospital stay.

The influence of these new developments on the surgical management of children with hyperparathyroidism has not thus far been well documented. In this article we describe characteristic features of PHPT in children and discuss how new technologies developed for and commonly used in adult patients shape the current trends in the management of PHPT in children.

Incidence and Prevalence

PHPT in children is a rare disease with a prevalence of 2–5 in 100,000 [10]. Many publications from the 1970s and 1980s [8, 11–14] misquoted this figure as incidence, further adding to the confusion of how common this condition in children really is. In comparison with the prevalence of PHPT in adults, quoted as 1–4 in 1,000 [1], PHPT in children is 100 times less frequent. The only attempt to establish incidence of PHPT in children comes from the French study by Mallet et al. [3], who estimated it as 1 case per 300,000 live births. A comparison with the incidence in adults, generally quoted at 30 per 100,000 [1], confirms the rarity of this condition. Even the largest published studies do not describe more than 52 children, typically operated on over 2–3 decades, and parathyroidectomies in children constituted only 0.7–3% of parathyroidectomies in adults performed in large, tertiary centres [3, 15, 16]. In our centre we operated on 29 children in the last 35 years [17].

Aetiology

PHPT in children has a bimodal age distribution, which reflects its different aetiology in very young and older children.

In neonates and infants it is caused exclusively by inactivating mutations of the calcium sensing receptor (CaSR) gene located on chromosome 3q which is inherited in an autosomal dominant way [18]. The CaSR is present on many cells but it is functionally important on the cells of parathyroids and kidneys. Neonates, who are homozygous for these functionally inactivating mutations, develop neonatal severe hyperparathyroidism (NSHPT). They present with very high parathyroid hormone (PTH) levels, causing increased osteoclastic activity, hypercalcaemia and a severe bone disease. Reduced calcium excretion at the distal nephron results in hypocalciuria despite high serum calcium levels. NSHPT is therefore known as ‘bones but not stones’ hyperparathyroidism. Heterozygous children, who either inherited CaSR mutation from one of their parents or developed *de novo* mutation, typically have a more benign form of neonatal hyperparathyroidism known as familial hypocalcuric hypercalcaemia (FHH). FHH is characterised by mild asymptomatic hypercalcaemia with paradoxically low urinary calcium and does not normally require treatment.

In older children and adolescents, PHPT is caused by the development of either adenoma or hyperplasia of the

parathyroid glands and can be sporadic (65–70%) or familial (27–31%). Parathyroid carcinoma in children is very rare, with only few cases reported in the literature [19, 20].

In children with sporadic PHPT, similarly to adults, the commonest pathology reported in the current literature is a solitary parathyroid adenoma (67–100%). External beam radiotherapy to the neck in early childhood is associated with an increased risk of developing hyperparathyroidism later in life. Children with familial PHPT have either multiple adenomas or hyperplasia involving all glands. Familial causes include multiple endocrine neoplasia types 1 and 2a (MEN1, MEN2a), hyperparathyroidism-jaw tumour (HPT-JT) syndrome and familial isolated hyperparathyroidism (FIHPT; table 1). In MEN1, hyperparathyroidism is the commonest manifestation. Typical age of onset is 20–25 years, with almost 100% penetrance by the age of 50 years [21]. It is rare before the age of 15 years but has been reported in children as young as 5 years. The incidence of PHPT in MEN2a is lower (20%) and is often caused by a single adenoma, though multigland hyperplasia can occur. Hyperparathyroidism associated with MEN2a has been diagnosed in children as young as 5 years of age (codon 634), but in the majority of patients it will develop in the 3rd and 4th decade. HPT-JT syndrome, caused by the HRPT2/CDC73 mutation, is most commonly associated with single gland disease and carries a 10–15% risk of parathyroid carcinoma [21]. FIHPT is diagnosed when hyperparathyroidism is present in a patient with a history of at least one first-degree relative affected, in the absence of other endocrine disorders or a family history of MEN. Mutations in families with FIHPT have been detected in the MEN, HRPT2/CDC73 and CaSR genes and the disease can involve single or multiple parathyroids [22].

Clinical Presentation

Table 2 summarises the symptoms reported in neonates and older children with PHPT. Neonates with NSHPT are all symptomatic and present with a variety of symptoms, including hypotonia and gastrointestinal and neurological symptoms frequently associated with severe bone demineralisation and skeletal abnormalities. A characteristic feature of PHPT in older children is late presentation, with at least 80% of children having symptoms and features of end organ damage prior to the diagnosis [2–6, 8, 9]. This is in sharp contrast to adults, where the majority of patients (80%) are diagnosed on routine

Table 1. Familial causes of primary hyperparathyroidism

Condition	Inheritance and mutation	Organs affected
MEN1	Autosomal-dominant MEN1 gene on chromosome 11	Parathyroid (90%), neuroendocrine tumours of the pancreas and gastrointestinal tract (60%), pituitary adenomas (30%), neuroendocrine tumours of the thymus and bronchus, adrenal hyperplasia and adenomas, lipomas, leiomyomas, and skin disorders such as angiofibromas and collagenomas
MEN2A	Autosomal-dominant MEN2A gene on chromosome 10	Parathyroid (20–30%), medullary thyroid carcinoma and adrenal pheochromocytomas
HPT-JT	Autosomal-dominant HRPT2/CDC73 gene on chromosome 1	Mainly hyperparathyroidism and fibro-osseous lesions of the mandible and maxilla; risk of parathyroid carcinoma in 10–15%; associated with renal lesions: renal cell carcinoma, Wilms tumour, hamartomas and cysts
FIHPT	Different mutations: MEN1, CaSR, HRPT2/CDC73	Parathyroid gland
FHH/NSHPT	Autosomal-dominant CaSR gene	Parathyroid gland

blood tests and are asymptomatic. Symptoms in children can be vague and non-specific, frequently affecting gastrointestinal, renal, musculoskeletal, and neurological systems. Delayed diagnosis could be a consequence of calcium levels not being part of routine blood tests in children, thereby resulting in later and more symptomatic presentations. This, interestingly, draws parallels with PHPT diagnosis in adults in previous decades, when routine calcium measurement was not the norm and most patients had symptoms at diagnosis [1]. More frequent measurement of calcium and PTH in children with otherwise unexplained symptoms could lead to earlier diagnosis and fewer complications.

Investigations

Biochemical Diagnosis. The biochemical diagnosis of PHPT is established by measuring serum calcium and PTH levels. The original competitive radioimmunoassay using bovine PTH measured not only the biologically active PTH but also inactive breakdown products and had poor sensitivity and specificity. The new generation of ‘intact PTH’ assays developed after 1987 are more sensitive, and PTH levels can now be measured with high accuracy in less than 15 min. Routine assessment of children with hypercalcaemia should include renal function

tests, 1,25-hydroxyvitamin D and 25-hydroxyvitamin D levels, bone density scan, and ultrasound of the kidneys. In children presenting without symptoms, with mild hypercalcaemia, marginally elevated PTH and hypocalcaemia, the diagnosis of FHH should be excluded. This is important, as FHH is a benign disease with no end organ damage and does not need treatment. The measurement of the calcium/creatinine ratio is a sensitive method for confirming FHH, and genetic testing for mutations of the CaSR could be used in ambiguous cases [23].

Genetic Mutations. Genetic mutations are found in 24–46% of children with PHPT, so familial hyperparathyroidism is much more common than in adults (1–2%) [2–4, 17]. The role of genetic screening in children with confirmed hyperparathyroidism is crucial, and current UK guidelines recommend the routine genetic testing of all children diagnosed with PHPT [24, 25]. A positive genetic test is helpful in establishing diagnosis, planning treatment and initiating biochemical and genetic screening of siblings and parents. All neonates with high calcium should undergo screening for CaSR mutations. In older children, testing for mutations should start with the MENIN gene, followed by the parafibromin (HRPT2/CDC73) gene in the event of the former test being normal, if there is a family history of HPT-JT or if the gland is an atypical adenoma or carcinoma. RET mutation analysis is recommended for children with features consistent

Table 2. Summary of current evidence for demographics, presentation and outcomes of investigations for children affected by PHPT

Published series	Demographics and diagnosis	Symptoms	Imaging
<i>Neonates with NSHP</i>			
Mallet [3], 2008 11 neonates	Age: not documented 4 M:7 F	All symptomatic (hypotonia 54%, poor feeding 18%, respiratory 27%, skeletal)	US useful in 3 out of 11 neonates
Al-Shanafey [7], 2010 5 neonates	Age: 7–30 days 3 M:2 F	All symptomatic (lethargy, poor feeding, irritability)	US, MIBI, CT: all negative
Alagaratnam [17], 2014 6 neonates (our series)	Age: 3 days to 4 months 3 M:3 F	All symptomatic GI 4, skeletal 3, neurological 4	US 4, MIBI 2: all negative
<i>Older children with PHPT</i>			
Allo et al. [13], 1982 (1971–1980)	53 patients (1 neonate) Age: 0–30 years (a third <18 years) 30 M:23 F	90% symptomatic (renal stones 50%, malaise/fatigue 30%, hypertension 17%, musculoskeletal 6%)	Not documented
Lawson [8], 1996 (1973–1995) Toronto	11 children (all sporadic) Age: 12–18 years 5 M:6 F	91% symptomatic (renal stones 45%, abdominal 18%, learning difficulties 18%, musculoskeletal 9%, fatigue 9%)	Venous sampling and angiography. successful in 3, US in 3/7, MIBI 1/1, CT 0/2, MRI 0/2
Kollars [2], 2005 (1970–2000) Mayo Clinic	52 children (36 sporadic, 16 familial) Age: 4.9–19 years 21 M:31 F	79% symptomatic (nonspecific 70%, abdominal 48%, renal stones 33%, polydipsia 21%)	42% US (sensitivity 86%, specificity 67%), 14% MRI, 8% CT, 6% MIBI, 2% angiography (accuracy not documented)
Libansky [6], 2008 (1996–2007) Prague	10 children (all sporadic) Age: 10–18 years 5 M:5 F	80% symptomatic (renal stones 50%, non-specific 30%, musculoskeletal 30%, abdominal 30%)	US (sensitivity 90%) MIBI (sensitivity 80%) CT, MRI (accuracy not documented)
Mallet [3], 2008 (1984–2004) France	44 children (41 sporadic, 3 familial) Age: 6–18 years 21 M:31 F	82% symptomatic (non-specific 71%, abdominal 43%, renal stones 41%, incidental 18%, musculoskeletal 16%, psychological 8%)	84% US, 43% MIBI, (sensitivity of combined US and MIBI 73%) 20% CT, 16% MRI
George [5], 2010 (1993–2006) Mumbai	18 children (all sporadic) Age: 13–20 years 4 M:14 F	95% symptomatic (musculoskeletal 89%, renal stones 39%, pancreatitis 6%)	95% US (sensitivity 55.5%) 83.3% CT (sensitivity 80%) 66.7% MIBI (sensitivity 90%)
Durkin [4], 2010 (2003–2009) Wisconsin	25 children (19 sporadic, 6 familial) Age: 10–25 years 4 M:6 F	64% symptomatic (renal stones 25%, fatigue 12%, abdominal 8%)	24% US (accuracy 50%), 72% MIBI (accuracy 61%)
Pashtan [9], 2013 (1990–2004) Chicago	21 children (20 sporadic, 1 familial) Age: 10–20 years 9 M:12 F	95% symptomatic (fatigue, depression, weakness 66%, renal stones 52%)	100% US (sensitivity 76%) MIBI (sensitivity 50%)
Burke [58], 2013 (2001–2012)	19 children (15 sporadic, 4 familial) Age: 10–19 years 7 M:12 F	Not documented	100% MIBI
Alagaratnam [17], 2014 (1978–2012) London (our series)	23 children (16 sporadic, 7 familial) Age: 7–16 years 12 M:11 F	90% symptomatic (gastrointestinal 8, skeletal 3, renal colic 2, depression 2)	20 US (sensitivity 93%) 16 MIBI (sensitivity 92%)
Imaging: number of children who had localization investigations and sensitivity %. US = Ultrasound.			

with MEN2a. An alternative to the sequential genetic screening described above would be to perform an analysis of all genetic mutations associated with hyperparathyroidism at once. The currently available panel of genetic tests includes MEN1 and 2, CaSR, HRPT2/CDC73, and CDKN 1A, 1B, 2B, and 2C, which is much cheaper than performing all these tests separately.

Imaging. Imaging of abnormal parathyroid glands is a critical part of the preoperative workup. Its role is to identify the position of enlarged glands in the neck or mediastinum and to differentiate between single and multiple gland disease. Investigations most commonly employed are ultrasound and MIBI (^{99m}Tc -methoxyisobutyl nitrile) scintigraphy (SPECT or PET). Table 2 summarises the

outcomes of the different imaging modalities for children affected by PHPT currently in the literature.

Ultrasound Scanning. Ultrasound scanning of the neck is usually performed using a high-frequency transducer (12–15 MHz), which enables the detection of enlarged parathyroid glands and a description of their size and position in relation to thyroid and other anatomical structures [26]. Adenomas typically appear as homogeneously echoic nodules on greyscale imaging. The use of colour Doppler confirms their high vascularity. Limitations of ultrasound include difficulty in identifying adenomas which are deep-seated (retrosternal/mediastinal) or related to air-filled structures such as the trachea and oesophagus [26]. In addition, ultrasound is an operator-dependent investigation, and therefore outcomes tend to relate to the level of experience of the centre and the individual radiologist. Younger children, who do not cooperate and cannot have ultrasound, should have this investigation done on the day of surgery under general anaesthetic just before the operation begins. A systematic review of 54 studies in adults [27] identified the sensitivity of ultrasound to be 78.55% in detecting solitary adenomas, 34.86% in hyperplasia and 16.20% in double adenomas. The largest case series in children with PHPT from the Mayo Clinic [2] reported ultrasound to have a sensitivity of 86%, specificity of 67% and a positive predictive value of 95% in identifying adenomatous and hyperplastic glands. Other reports describing the use of ultrasound in children with PHPT reported a sensitivity of 55–90% [5, 6]. In our hands, ultrasound predicted correct laterality of the abnormal glands in all older children, and its overall sensitivity and specificity were 93 and 98%, respectively. Ultrasound is not helpful in neonates with NSHPT and older children with familial hyperparathyroidism [17].

Nuclear Imaging. This is usually performed with MIBI, which avidly localises in the mitochondria present in large numbers in the oxyphil cells of parathyroid tissue, thyroid and salivary glands. Parathyroid adenomas, and to a lesser degree hyperplastic glands, demonstrate higher tracer uptake in the early image and delayed washout in the late image compared with the surrounding thyroid tissue [26]. The MIBI scan is often done in dual-phase imaging – an early planar image at 10–20 min and a delayed image at 90–120 min. The use of SPECT, which produces 3D images from two cameras, has been shown to improve its sensitivity. Nuclear imaging is better than ultrasound at detecting ectopic adenomas. However, in the presence of thyroid nodules, differentiation of the abnormal parathyroid and thyroid tissue can be difficult [27].

The systemic review of the use of MIBI in adults [27] reported a sensitivity of 88.44% in detecting solitary adenomas, 44.46% in detecting hyperplastic glands and 29.95% in detecting double adenomas. In children, MIBI scanning is used frequently and has a sensitivity of 60–90% [5, 6, 9]. Combined ultrasound and MIBI scanning has an overall sensitivity of 73% [3] and 95% [28, 29] in detecting solitary adenomas. In our hands, the sensitivity and specificity of MIBI in children with sporadic PHPT were 92 and 97%, respectively, but they were less helpful in children with familial PHPT [17].

CT, MRI and Venous Sampling. These are rarely required in paediatric practice and should be reserved for cases where ultrasound and MIBI are negative or in recurrent hyperparathyroidism which requires reoperation. Axial, thin-cut, contrast-enhanced CT images from the base of the skull through the mediastinum can help to identify abnormal parathyroids in the neck not seen on other scans and ectopic glands in the mediastinum [27]. MRI is limited by similar appearances of cervical lymph nodes and parathyroid adenomas, and venous sampling is an invasive test, which is now almost completely obsolete in children with PHPT.

Management of Children with PHPT

The aim of medical management in children with PHPT is to control hypercalcaemia. Neonates with NSHPT require urgent medical attention, as this condition is associated with high rates of morbidity and mortality in untreated cases. Historically, emergency parathyroidectomy was the only life-saving treatment. Recently, NSHPT has been shown to have varying degrees of severity linked to the type of CaSR mutation, with some less severe forms responding to medical management [3, 30]. Hyperhydration, diuretics, low calcium diet, bisphosphonates, and calcitonin lower calcium levels in patients with inactivating mutations as these treatments use mechanisms not depending on CaSR. Cinacalcet, however, is an allosteric modulator and enhances signal transduction and CaSR activation. Its effectiveness depends on the preservation of the tridimensional structure of the receptor, and in vivo studies showed variable effect on receptor function in different mutations. This possibly explains why the use of cinacalcet can cause rapid and sustained reduction of calcium and PTH in heterozygous but not homozygous children. Medical treatment able to control calcium and PTH levels can be used to stabilise neonates before surgery and can alleviate the need for surgery in

milder cases of NSHPT. Some of these children will normalise their calcium and PTH over a period of years, and their biochemical and clinical phenotype will resemble FHH [3, 30]. However, if medical treatment fails to control high calcium, surgery remains the preferred curative treatment option, especially in children who fail to thrive, have repeated admissions for the treatment of hypercalcaemia or develop severe bone disease.

Medical management of older children presenting with PHPT depends on the severity of hypercalcaemia. Children with high calcium (>3 mmol/l), especially if unwell, require admission to hospital for rehydration, diuretics and infusion of bisphosphonates. Asymptomatic children with moderate hypercalcaemia should have their investigations done as early as possible without specific attempts to lower the calcium. There is no place for long-term conservative management of children with PHPT and most children should be promptly scheduled for surgery.

Surgery for PHPT

The aims of surgery in children with PHPT are immediate and permanent cure of abnormally high levels of calcium and PTH, alleviation of the symptoms and prevention or reversal of end organ damage. The choice of operating technique, which includes bilateral neck exploration (BNE) or MIP, depends on the underlying parathyroid pathology and imaging results indicating the number and location of glands to be removed (1–4). In children who need removal of 1–3 abnormal glands, normalisation of calcium and PTH levels without postoperative supplementation is the goal. In children where all 4 glands are abnormal and have to be removed, the goal is normocalcaemia maintained either by calcium and vitamin D3 supplementation or autotransplantation of parathyroid tissue.

BNE of all 4 parathyroid glands, irrespective of the underlying parathyroid pathology, has been the gold standard surgical treatment for many past decades. Typically, BNE is performed through a collar incision, with exposure and dissection of all the parathyroid glands prior to deciding which glands should be removed. BNE allows not only direct visualisation of the 4 glands but also enables exploration of sites of potential ectopic glands, including the tracheoesophageal groove, thyroid gland, thyrothymic ligament, retroesophageal region, and carotid sheath [31]. Deciding which glands are abnormal and need removing is based on prior knowledge of preoperative imaging and the size of the glands observed during surgery. In children, BNE remains the operation of choice in the following three

distinct scenarios: (1) in familial PHPT when multiple glands are expected to be abnormal, (2) when all imaging is negative and (3) when MIP fails to identify the enlarged gland and, thereby, conversion to BNE is necessary.

In neonates with NSHPT, parathyroidectomy of 4 glands is essential to achieve cure; in our experience removal of less than 4 glands results in persistently high levels of calcium and PTH [17]. Some authors recommend parathyroid autotransplantation, but very often these grafts fail to work [3, 7]. In MEN1, parathyroidectomy of 4 glands is usually recommended as subtotal (less than 4 glands) parathyroidectomy is associated with unacceptably high rates of recurrent hypercalcaemia requiring further surgery. [32] In MEN2a, removal of 1–3 glands can be curative [33] without the risk of permanent hypocalcaemia. HPT-JT syndrome has a 15% risk of parathyroid carcinoma, and surgical options include the removal of the single abnormal gland with subsequent annual surveillance of calcium and PTH levels [34] or prophylactic total parathyroidectomy to prevent future malignancy or recurrent HPT [32]. FIHPT is a complex disease associated with mutations in different genes, including CaSR, MEN1 and HRPT2/CDC73. The current recommendation is to remove 1–4 abnormal glands using intraoperative PTH (IOPTH) monitoring and to consider autotransplantation [34].

In adults, until the recent introduction of the minimally invasive approach, BNE has been a standard procedure which cured 95% of patients, with complication rates less than 4% [31]. BNE is the most commonly reported procedure in children and in the two largest series describing 52 and 44 cases, respectively, with sporadic and familial HPT, all children underwent BNE [2, 3]. Overall, 83 and 89% of children in these series were cured, respectively. Although autotransplantations were carried out for multigland disease, the outcomes specifically regarding autotransplantation were not reported; 4–17% of the children described in the literature were not cured by the first operation and required further surgery (table 3). This was much more common in series describing children with familial hyperparathyroidism [2, 3, 17]. Children with sporadic PHPT are almost always cured by the first operation [4, 6, 9, 17]. Postoperative symptomatic hypocalcaemia was the commonest complication reported in 20–47% of children. Complications related to injury of recurrent laryngeal or other nerves in the neck are extremely rare – 1 child had transient hoarseness and 1 developed Horner syndrome [3].

Parathyroid autotransplantation, first described in 1926 [35], is a common and established practice when

Table 3. Surgical outcomes and histology of resected parathyroid glands in children with PHPT

Published series	Management	Histology	Outcomes
<i>With NSHPT</i>			
Mallet [3], 2008 11 neonates	Total parathyroidectomy 6 (2 autotransplantation) Conservative management 5	Hyperplasia all operated cases	1 child in the conservative management arm required surgery
Al-Shanafey [7], 2010 5 neonates	Total parathyroidectomy and autotransplantation in all cases	Hyperplasia all cases	1 vocal cord paralysis necessitating tracheostomy for few months
Alagaratnam [17], 2014 6 neonates (our series)	Total parathyroidectomy 5 Subtotal parathyroidectomy 1	Hyperplasia all cases	Persistent high calcium 1
<i>Older children with PHPT</i>			
Allo et al. [13], 1982 53 children	BNE all cases	Adenoma 35 Hyperplasia 17 Normal 1	Persistent hypercalcaemia 1 (subsequently identified to have a mediastinal adenoma)
Lawson [8], 1996 11 children	Probably BNE	Adenoma all cases	Transient hoarseness 1 Symptomatic hypocalcaemia 4 No recurrence
Kollars [2], 2005 52 children	BNE all cases	Adenoma 35 Hyperplasia 16	Symptomatic hypocalcaemia 24 (46%) Reoperation 9 (17%) due to ongoing hypercalcaemia/recurrence
Mallet [3], 2008 44 children	Not generally documented BNE and unilateral explorations guided by preoperative investigations	Adenoma 29 Hyperplasia 11	Symptomatic hypocalcaemia 39% Reoperation 5 (11%)
Libansky [6], 2008 10 children	BNE	Adenoma all cases	Symptomatic hypocalcaemia 2 No recurrence
George [5], 2010 18 children	Unilateral neck exploration all cases	Adenoma all cases	Symptomatic hypocalcaemia 27.7% Persistent high calcium 1
Durkin [4], 2010 25 children	Radio-guided MIP (17/18) Conversion to BNE 22%	Adenoma 15 Hyperplasia 10	No recurrence
Pashtan [9], 2013 21 children	BNE	Single gland disease 18 Multiple gland disease 3	Symptomatic hypocalcaemia Recurrence 1
Burke [58], 2013 19 children	Radio-guided MIP and BNE	Adenoma 14 Hyperplasia 5	No recurrence
Alagaratnam [17], 2014 29 children (our series)	BNE and MIP (IOPH)	Adenoma 21 Hyperplasia 6	Symptomatic hypocalcaemia Recurrence 1

normal parathyroids are incidentally removed during thyroidectomy. Autotransplanting abnormal parathyroid tissue is controversial and presents a dilemma. It is potentially desirable, since there is no direct hormonal replacement therapy available for the PTH, and the medical management of postoperative hypoparathyroidism requires vitamin D and calcium supplementation. However, transplanted abnormal parathyroid tissue could cause recurrence requiring more surgery. If autotransplantation is pursued, it can be carried out either during

the primary procedure or after cold storage (usually -135°C), usually within 24 months [35]. The excised gland is divided into multiple small pieces and placed in the sternocleidomastoid or the forearm muscles. An alternative procedure involves intramuscular injections of parathyroid glands [36]. Good graft function has been reported in 86–100% of adult patients [35, 37], but in children many transplants fail [3, 7].

The increasing role of MIP in treating patients with sporadic PHPT is a result of the growing acceptance that

solitary adenomas are responsible for the majority of cases, not only in adults but also in children. Improved accuracy of preoperative localisation studies allows precise identification of the site of the adenoma and enables targeted removal of the affected gland without the need for exposure or dissection of the remaining parathyroid glands.

There are two distinct techniques employed to perform MIP. The first is a mini-incision parathyroidectomy, which usually involves a small 1-inch incision overlying the affected parathyroid gland, blunt dissection of tissue and the removal of parathyroid adenoma under direct vision. The second technique uses an endoscope introduced either in the midline, laterally between the carotid sheath and the strap muscles, or via a transaxillary approach [38–41]. Endoscopic parathyroidectomy requires creation of space for the tip of the endoscope either by insufflation of carbon dioxide [39] or gasless retraction, as used by Miccoli et al. [42]. A survey published in 2000 by the International Association for Endocrine Surgeons (IAES) found that 59% of surgeons perform MIP in adults, with 92% using mini-incision, 22% video-assisted parathyroidectomy and 12% the gas insufflation technique [43]. Studies in adults have demonstrated that MIP can cure as many as 98% of patients – therefore its success rate is similar to BNE. Additional benefits of MIP are better cosmesis and a reduction in operating time and hospital stay, resulting in cost savings [44, 45].

The literature describing outcomes of MIP in children is limited. Durkin et al. [4] reported good outcomes of radio-guided MIP, and two case series reported the successful use of the transaxillary endoscopic approach [41, 46]. Taking into account the increasingly widespread use and good results of MIP in adults, further use of ‘keyhole’ parathyroidectomy in children is desirable. Current evidence suggests that good outcomes can be achieved by all minimally invasive techniques, but the endoscopic approach is complicated, has a high conversion rate and increased cost of equipment and is difficult to learn [31, 47]. We have reported the successful use of mini-incision MIP in children and would recommend this technique for all children with sporadic hyperparathyroidism [17].

Intraoperative Techniques Aiding Localisation and Confirmation of Cure

The failure of surgery to cure hyperparathyroidism is predominantly due to either multigland disease (hyperplasia, double adenomas) unrecognised by preoperative

localisation studies or the inability to find parathyroid glands in unusual locations (ectopic glands). Various operative adjuncts such as IOPTH monitoring, radio-guided parathyroidectomy, frozen section, and methylene blue are commonly used to overcome this problem and improve the cure rate.

Frozen Section. Frozen section of resected specimens is the oldest and most widely used technique to confirm that removed tissue is a parathyroid gland and has a 99.2% accuracy in differentiating parathyroid from non-parathyroid tissue [48, 49]. It is not reliable in distinguishing an adenoma from multigland hyperplasia. The main shortcoming of frozen section is its inability to determine whether the remaining parathyroid glands function normally and, therefore, it is unable to confirm cure.

Methylene Blue. Injected intravenously approximately an hour before surgery, methylene blue has been widely used to aid intraoperative localisation of parathyroid glands in adults. The evidence from retrospective studies [50] suggests that though operative times are reduced, the use of methylene blue does not demonstrate a significant improvement in the cure rate or recurrence of hyperparathyroidism. Methylene blue has a similar structure to monoamine oxidase inhibitors and has been reported to cause serotonin syndrome in patients taking selective serotonin reuptake inhibitors [51]. It can also cause neurotoxicity, manifesting as toxic metabolic encephalopathy. The European Society of Endocrine Surgeons recommends limiting its use in parathyroid surgery in adults [52], and in our view it should not be used in children.

Fluorescence-Guided Parathyroidectomy. Similarly to methylene blue, this is used to differentiate the normal and enlarged parathyroid glands. Patients take oral aminolevulinic acid 4–5 hours prior to surgery. The operating field is illuminated with violet-blue light (405-nm wavelength), to which the parathyroid glands selectively demonstrate red fluorescence [53]. Initial case series [53, 54] report good ability to identify the parathyroid glands, but potential side effects include skin sensitivity to normal light (patients remain in hospital for 24–28 h after the procedure in dim-lit rooms to avoid this), transient elevation in liver enzymes, nausea, and vomiting. More evidence needs to become available from adult studies before this technique can be considered in children.

Radio-Guided Parathyroidectomy. This involves the injection of MIBI preoperatively and the use of a portable γ -probe during surgery to localise the abnormal parathyroid in vivo and to determine the ex vivo radioactivity count after the excision. Parathyroid adenomas have a count which is 59% above the background activity, while

thyroid and hyperplastic glands are less than 16% above background activity. Using a cut-off of 20% with a positive MIBI scan preoperatively, the excision of an abnormal parathyroid could be confirmed [55]. In patients where the excised gland does not meet the count criteria of >20% of the background count, further exploration of the contralateral side is performed through the same incision. In adults, reported success rates have been as high as 93–97% [50, 56]. Radio-guided parathyroidectomy can also be successfully performed regardless of whether preoperative MIBI scans are positive or negative [57]. Radio-guided parathyroidectomy in conjunction with IOPTH monitoring was used by Durkin et al. [4] in 25 children, 18 of whom had MIP attempted. The abnormal parathyroids were successfully removed in 78% of cases, but conversion to BNE (22%) was high due to the failure of normalisation of IOPTH levels. More recently, Burke et al. [58] reported successful radio-guided parathyroidectomy in 19 children. Radio-guided parathyroidectomy, however, increases exposure to radiation and should be used with caution in children. In our recent practice, all children with sporadic PHPT had successful mini-incision MIP in conjunction with IOPTH monitoring. In our view, the intraoperative use of radioactivity in parathyroid surgery is unnecessary. An IAES survey also reported that only 16% of members employ this technique [43]. We recommend that MIP in conjunction with IOPTH monitoring is the most appropriate for young patients, and in our view it should now be considered the operation of choice in children.

IOPTH Monitoring. IOPTH monitoring was first reported in 1988 [59]. Its concept is based on the physiology of PTH, which in patients with normal renal function has a biological half-life of less than 5 min. Therefore, the removal of the abnormal, hypersecreting parathyroid gland results in a rapid reduction in the PTH levels in the blood stream [60]. Blood sampling is done before excision and at 5 and 10 min after excision of the abnormal parathyroid, and biochemical cure is confirmed by 50% reduction of PTH compared with the highest pre-excision level. Measurements are done in the operating theatre next to the patient and take 12 min. IOPTH is the simplest and most effective technique of confirming the cure and success of the operation. It helps to overcome the inaccuracies of preoperative localisation studies in situations where multigland disease has been missed. Persistently high PTH levels indicate that not all abnormal parathyroids were removed and that further exploration and resection of hypersecreting parathyroids is necessary. IOPTH is most helpful in patients with discordant ultra-

sound and MIBI findings, patients who have had single preoperative localisation study (i.e. only ultrasound in pregnant women) and in reoperations for recurrent hyperparathyroidism [50]. IOPTH changed the operative management in only 2% of cases with concordant ultrasound and MIBI but in 74% of cases with discordant imaging [61]. IOPTH assays in the removed specimen can also be used to differentiate between parathyroid and non-parathyroid tissues; however, frozen section may be superior for this purpose [62]. IOPTH monitoring is routinely used by 68% of the members of IAES [43]. Evidence of IOPTH in children is very limited and has been described in only 3 studies [4, 9, 17]. Durkin et al. [4] used it in conjunction with radio-guided parathyroidectomy and Pashtan et al. [9] with BNE. Our group was the first to report the successful use of IOPTH monitoring in children undergoing mini-incision MIP.

Conclusions

New trends in the surgical management of children with PHPT are shaped by innovative solutions in diagnostics, genetics, imaging, and surgical techniques, which have proved their value in adult patients. It is desirable that surgical experience gained from treating adults will benefit children. PHPT in children differs from PHPT in adults in that it is rare, equally common in girls and boys, more frequently familial, and almost always symptomatic. Despite these differences, biochemical and genetic testing as well as preoperative localisation studies have the same accuracy and value in both groups. Sporadic PHPT in children, similarly to adults, is caused in the great majority of cases by single parathyroid adenoma and can be cured by MIP. Children with familial PHPT should undergo BNE and removal of multiple abnormal parathyroid glands. IOPTH monitoring is the most promising technique in aiding the decision about the number of parathyroids needing removal and confirming cure.

References

- 1 Fraser WD: Hyperparathyroidism. *Lancet* 2009;374:145–158.
- 2 Kollars J, Zarroug AE, van Heerden J, Lteif A, Stavlo P, Suarez L, Moir C, Ishitani M, Rodeberg D: Primary hyperparathyroidism in pediatric patients. *Pediatrics* 2005;115:974–980.
- 3 Mallet E; Working Group on Calcium Metabolism: Primary hyperparathyroidism in neonates and childhood. *The French experience (1984–2004)*. *Horm Res* 2008;69:180–188.

- 4 Durkin ET, Nichol PF, Lund DP, Chen H, Sippel RS: What is the optimal treatment for children with primary hyperparathyroidism? *J Pediatr Surg* 2010;45:1142–1146.
- 5 George J, Acharya SV, Bandgar TR, Menon PS, Shah NS: Primary hyperparathyroidism in children and adolescents. *Indian J Pediatr* 2010;77:175–178.
- 6 Libansky P, Astl J, Adamek S, Nanka O, Pafko P, Spackova J, Foltan R, Sedy J: Surgical treatment of primary hyperparathyroidism in children: report of 10 cases. *Int J Pediatr Otorhinolaryngol* 2008;72:1177–1182.
- 7 Al-Shanafey S, Al Hosaini R, Al Ashwal A, Al Rabeeah A: Surgical management of severe neonatal hyperparathyroidism: one center's experience. *J Pediatr Surg* 2010;45:714–717.
- 8 Lawson ML, Miller SF, Ellis G, Filler RM, Kooh SW: Primary hyperparathyroidism in a paediatric hospital. *QJM* 1996;89:921–932.
- 9 Pashtan I, Grogan RH, Kaplan SP, Devon K, Angelos P, Liu D, Kaplan EL: Primary hyperparathyroidism in adolescents: the same but different. *Pediatr Surg Int* 2013;29:275–279.
- 10 Kruse K: Disorders of calcium and bone metabolism; in Charles Brook (ed): *Clinical Pediatric Endocrinology*. London, Blackwell Science, 1995, pp 735–778.
- 11 Mannix H Jr: Primary hyperparathyroidism in children. *Am J Surg* 1975;129:528–531.
- 12 Rapaport D, Ziv Y, Rubin M, Huminer D, Dintsman M: Primary hyperparathyroidism in children. *J Pediatr Surg* 1986;21:395–397.
- 13 Allo M, Thompson NW, Harness JK, Nishiyama RH: Primary hyperparathyroidism in children, adolescents, and young adults. *World J Surg* 1982;6:771–776.
- 14 Girard RM, Belanger A, Hazel B: Primary hyperparathyroidism in children. *Can J Surg* 1982;25:11–32.
- 15 Harman CR, van Heerden JA, Farley DR, Grant CS, Thompson GB, Curlee K: Sporadic primary hyperparathyroidism in young patients: a separate disease entity? *Arch Surg* 1999;134:651–655.
- 16 Loh KC, Duh QY, Shoback D, Gee L, Siperstein A, Clark OH: Clinical profile of primary hyperparathyroidism in adolescents and young adults. *Clin Endocrinol (Oxf)* 1998;48:435–443.
- 17 Alagaratnam S, Brain C, Spoudeas HA, Dattani MT, Hindmarsh P, Allgrove J, Van't Hoff W, Kurzawinski TR: Surgical treatment of children with hyperparathyroidism: single centre experience. *J Pediatr Surg* 2014;49:1539–1543.
- 18 Lietman SA, Germain-Lee EL, Levine MA: Hypercalcemia in children and adolescents. *Curr Opin Pediatr* 2010;22:508–515.
- 19 Meier DE, Snyder WH, III, Dickson BA, Margraf LR, Guzzetta PC Jr: Parathyroid carcinoma in a child. *J Pediatr Surg* 1999;34:606–608.
- 20 Hamill J, Maoate K, Beasley SW, Corbett R, Evans J: Familial parathyroid carcinoma in a child. *J Paediatr Child Health* 2002;38:314–317.
- 21 DeLellis RA, Mazzaglia P, Mangray S: Primary hyperparathyroidism: a current perspective. *Arch Pathol Lab Med* 2008;132:1251–1262.
- 22 Kandil E, Alabbas HH, Lum YW, Tufaro AP: Familial isolated primary hyperparathyroidism with double adenoma. *South Med J* 2010;103:236–238.
- 23 Christensen SE, Nissen PH, Vestergaard P, Heickendorff L, Brixen K, Mosekilde L: Discriminative power of three indices of renal calcium excretion for the distinction between familial hypocalciuric hypercalcaemia and primary hyperparathyroidism: a follow-up study on methods. *Clin Endocrinol (Oxf)* 2008;69:713–720.
- 24 Crowne E, Brain CB, Murday V, Harrison B, Squire R, Buchanan C, Hindmarsh PC, Spoudeas HA: Hyperparathyroidism and pituitary tumours in association with multiple endocrine neoplasia type 1 (MEN1) syndrome; in Spoudeas HA (ed): *Paediatric Endocrine Tumours. A multi-disciplinary consensus statement of best practice from a working group convened under the auspices of the BSPED and UKCCSG (rare tumour working groups)*. Crawley, Novo Nordisk, 2005, pp 107–120.
- 25 Murday V, Brain CB, Crowne E, Harrison B, Squire R, Buchanan C, Spoudeas HA: Medullary thyroid carcinoma (MTC) and multiple endocrine neoplasia type 2 (MEN 2) syndromes; in Spoudeas HA (ed): *Paediatric endocrine tumours. A multi-disciplinary consensus statement of best practice from a working group convened under the auspices of the BSPED and UKCCSG (rare tumour working groups)*. Crawley, Novo Nordisk, 2005, pp 93–106.
- 26 Patel CN, Scarsbrook AF: Multimodality imaging in hyperparathyroidism. *Postgrad Med J* 2009;85:597–605.
- 27 Ruda JM, Hollenbeak CS, Stack BC Jr: A systematic review of the diagnosis and treatment of primary hyperparathyroidism from 1995 to 2003. *Otolaryngol Head Neck Surg* 2005;132:359–372.
- 28 Lumachi F, Zucchetta P, Marzola MC, Boccagni P, Angelini F, Bui F, D'Amico DF, Favia G: Advantages of combined technetium-99m-sestamibi scintigraphy and high-resolution ultrasonography in parathyroid localization: comparative study in 91 patients with primary hyperparathyroidism. *Eur J Endocrinol* 2000;143:755–760.
- 29 Patel CN, Salahudeen HM, Lansdown M, Scarsbrook AF: Clinical utility of ultrasound and ^{99m}Tc sestamibi SPECT/CT for preoperative localization of parathyroid adenoma in patients with primary hyperparathyroidism. *Clin Radiol* 2010;65:278–287.
- 30 Waller S, Kurzawinski T, Spitz L, Thakker R, Cranston T, Pearce S, Cheetham T, van't Hoff WG: Neonatal severe hyperparathyroidism: genotype/phenotype correlation and the use of pamidronate as rescue therapy. *Eur J Pediatr* 2004;163:589–594.
- 31 Augustine MM, Bravo PE, Zeiger MA: Surgical treatment of primary hyperparathyroidism. *Endocr Pract* 2011;17(suppl 1):75–82.
- 32 Stalberg P, Carling T: Familial parathyroid tumors: diagnosis and management. *World J Surg* 2009;33:2234–2243.
- 33 Scholten A, Schreinemakers JM, Pieterman CR, Valk GD, Vriens MR, Borel R: Evolution of surgical treatment of primary hyperparathyroidism in patients with multiple endocrine neoplasia type 2A. *Endocr Pract* 2011;17:7–15.
- 34 Landry CS, Waguespack SG, Perrier ND: Surgical management of nonmultiple endocrine neoplasia endocrinopathies: state-of-the-art review. *Surg Clin North Am* 2009;89:1069–1089.
- 35 Moffett JM, Suliburk J: Parathyroid autotransplantation. *Endocr Pract* 2011;17(suppl 1):83–89.
- 36 Tan CC, Cheah WK, Tan CT, Rauff A: Intramuscular injection of parathyroid autografts is a viable option after total parathyroidectomy. *World J Surg* 2010;34:1332–1336.
- 37 Feldman AL, Sharaf RN, Skarulis MC, Bartlett DL, Libutti SK, Weinstein LS, Marx SJ, Norton JA, Fraker DL, Alexander HR: Results of heterotopic parathyroid autotransplantation: a 13-year experience. *Surgery* 1999;126:1042–1048.
- 38 Lobe TE, Wright SK: The transaxillary, totally endoscopic approach for head and neck endocrine surgery in children. *J Laparoendosc Adv Surg Tech A* 2011;21:97–100.
- 39 Gagner M: Endoscopic subtotal parathyroidectomy in patients with primary hyperparathyroidism. *Br J Surg* 1996;83:875.
- 40 Henry JF, Sebag F, Tamagnini P, Forman C, Silaghi H: Endoscopic parathyroid surgery: results of 365 consecutive procedures. *World J Surg* 2004;28:1219–1223.
- 41 Dutta S, Slater B, Butler M, Albanese CT: 'Stealth surgery': transaxillary subcutaneous endoscopic excision of benign neck lesions. *J Pediatr Surg* 2008;43:2070–2074.
- 42 Miccoli P, Bendinelli C, Conte M, Pinchera A, Marocchi C: Endoscopic parathyroidectomy by a gasless approach. *J Laparoendosc Adv Surg Tech A* 1998;8:189–194.
- 43 Sackett WR, Barraclough B, Reeve TS, Delbridge LW: Worldwide trends in the surgical treatment of primary hyperparathyroidism in the era of minimally invasive parathyroidectomy. *Arch Surg* 2002;137:1055–1059.
- 44 Udelsman R: Six hundred fifty-six consecutive explorations for primary hyperparathyroidism. *Ann Surg* 2002;235:665–670.
- 45 Nilsen FS, Haug E, Heidemann M, Karlsen SJ: Does rapid intraoperative parathyroid hormone analysis predict cure in patients undergoing surgery for primary hyperparathyroidism? A prospective study. *Scand J Surg* 2006;95:28–32.
- 46 Lobe TE, Wright SK: The transaxillary, totally endoscopic approach for head and neck endocrine surgery in children. *J Laparoendosc Adv Surg Tech A* 2011;21:97–100.

- 47 Miccoli P, Berti P, Materazzi G, Massi M, Piccone A, Minuto MN: Results of video-assisted parathyroidectomy: single institution's six-year experience. *World J Surg* 2004;28:1216–1218.
- 48 Westra WH, Pritchett DD, Udelsman R: Intraoperative confirmation of parathyroid tissue during parathyroid exploration: a retrospective evaluation of the frozen section. *Am J Surg Pathol* 1998;22:538–544.
- 49 Saxe AW, Baier R, Tesluk H, Toreson W: The role of the pathologist in the surgical treatment of hyperparathyroidism. *Surg Gynecol Obstet* 1985;161:101–105.
- 50 Harrison BJ, Triponez F: Intraoperative adjuncts in surgery for primary hyperparathyroidism. *Langenbecks Arch Surg* 2009;394:799–809.
- 51 Pollack G, Pollack A, Delfiner J, Fernandez J: Parathyroid surgery and methylene blue: a review with guidelines for safe intraoperative use. *Laryngoscope* 2009;119:1941–1946.
- 52 Bergenfelz AO, Hellman P, Harrison B, Sitges-Serra A, Dralle H: Positional statement of the European Society of Endocrine Surgeons (ESES) on modern techniques in pHPT surgery. *Langenbecks Arch Surg* 2009;394:761–764.
- 53 Suzuki T, Numata T, Shibuya M: Intraoperative photodynamic detection of normal parathyroid glands using 5-aminolevulinic acid. *Laryngoscope* 2011;121:1462–1466.
- 54 Prosst RL, Weiss J, Hupp L, Willeke F, Post S: Fluorescence-guided minimally invasive parathyroidectomy: clinical experience with a novel intraoperative detection technique for parathyroid glands. *World J Surg* 2010;34:2217–2222.
- 55 Murphy C, Norman J: The 20% rule: a simple, instantaneous radioactivity measurement defines cure and allows elimination of frozen sections and hormone assays during parathyroidectomy. *Surgery* 1999;126:1023–1028.
- 56 Rubello D, Mariani G, Pelizzo MR: Minimally invasive radio-guided parathyroidectomy on a group of 452 primary hyperparathyroid patients: refinement of preoperative imaging and intraoperative procedure. *Nuklearmedizin* 2007;46:85–92.
- 57 Chen H, Sippel RS, Schaefer S: The effectiveness of radioguided parathyroidectomy in patients with negative technetium Tc-99m-sestamibi scans. *Arch Surg* 2009;144:643–648.
- 58 Burke JF, Jacobson K, Gosain A, Sippel RS, Chen H: Radioguided parathyroidectomy effective in pediatric patients. *J Surg Res* 2013;184:312–317.
- 59 Nussbaum SR, Thompson AR, Hutcheson KA, Gaz RD, Wang CA: Intraoperative measurement of parathyroid hormone in the surgical management of hyperparathyroidism. *Surgery* 1988;104:1121–1127.
- 60 Carter AB, Howanitz PJ: Intraoperative testing for parathyroid hormone: a comprehensive review of the use of the assay and the relevant literature. *Arch Pathol Lab Med* 2003;127:1424–1442.
- 61 Hwang RS, Morris LF, Ro K, Park S, Ituarte PH, Hong JC, Yeh MW: A selective, Bayesian approach to intraoperative PTH monitoring. *Ann Surg* 2010;251:1122–1126.
- 62 Conrad DN, Olson JE, Hartwig HM, Mack E, Chen H: A prospective evaluation of novel methods to intraoperatively distinguish parathyroid tissue utilizing a parathyroid hormone assay. *J Surg Res* 2006;133:38–41.