Surgical treatment of children with hyperparathyroidism: Single centre experience

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ARTICLE INFO

Article history:
Received 17 November 2013
Received in revised form 20 May 2014
Accepted 25 May 2014

Key words:
Hyperparathyroidism
Parathyroid surgery in children
Parathyroidectomy
Parathyroid glands
Minimally invasive parathyroidectomy
Calcium sensing receptors

ABSTRACT

Background: Hyperparathyroidism (HPT) in children is rare and surgical management is supported only by limited evidence.

Methods: Retrospective case series of all children under the age of 16 years who underwent parathyroidectomy (PTx) between 1978 and 2012.

Results: We identified 29 children who had surgery for HPT. Six were neonates with neonatal severe hyperparathyroidism (NSHPT) and 23 older children (age range 7–16 years) with sporadic (16) or familial (7) HPT and 93% were symptomatic. Accuracy of ultrasound and Miibi in localising solitary parathyroid adenomas was 96%, but less helpful in hyperplasia and neonates. Children with NSHPT underwent 5 curative total and 1 subtotal PTx (no reoperations). Children with familial HPT underwent 3 total and 4 subtotal PTx. One child with subtotal PTx required a reoperation. Children with sporadic HPT underwent subtotal PTx prior to 1980 (2), exploration and removal of enlarged glands 1980–2002 (5) and minimally invasive PTx since 2002 (9) and all cured by the first operation.

Conclusions: Our study documents that HPT in children is predominantly symptomatic on presentation and genetically determined in 46% of cases. Imaging is accurate in localising solitary parathyroid adenomas, but not hyperplasias. Total PTx for familial HPT was curative and minimally invasive PTx is the operation of choice for older children with sporadic HPT.

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Hyperparathyroidism (HPT) affects both children and adults but it is rare in the former and common in latter [1–5]. In sharp contrast to only a handful of small case series of children with HPT described in the literature [2,4–6], there is a significant body of evidence about HPT in adults concerned with its epidemiology, symptoms, accuracy of imaging and surgical outcomes [7,8]. Management of hyperparathyroidism in adults has seen a sea of change in the last two decades [7,8].

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at our institution between 1978 and 2012. Demographic data collected were gender, age at diagnosis and age at the time of surgery. Fisher's exact test was used to assess gender distribution and the independent sample t-test for age differences.

Causes of HPT were classified as genetically determined (familial) or sporadic and, wherever possible, details of the mutations were reported. The clinical presentations were classified in the following categories: gastrointestinal, skeletal, renal, neurological/psychological or as asymptomatic. The laboratory measurements reviewed were serum calcium and parathyroid hormone concentration at presentation and after the operation.

Pre-operative localisation studies reviewed were ultrasonography (US), technetium 99m sestamibi parathyroid scintigraphy (MIBI) and parathyroid venous sampling (PVS). Their value was expressed as sensitivity, specificity and overall accuracy of their ability to identify firstly the laterality of the abnormal glands (left/right), and secondly to predict the precise quadrant position of abnormal glands (i.e. left/upper and right/lower). Accuracy of US and MIBI in distinguishing single from multiple gland disease was also calculated. Findings of the imaging were compared to findings at surgery and histology, which were considered 'gold standard'.

Operations were classified either as minimally invasive parathyroidectomy (MIP) or bilateral neck exploration (BNE). Minimally invasive parathyroidectomy was defined as an operation during which a single abnormal parathyroid gland was removed through a small lateral incision without an attempt to visualize other glands. Bilateral neck exploration was performed through a skin crease collar incision, which allowed direct visualisation of all and removal of abnormal glands. Histology of the removed glands was reported as adenoma, hyperplasia or normal. Surgical outcomes were determined by postoperative complications classified as bleeding, infection, voice change, hypocalcaemia and the need for re-operation. Length of follow up was recorded.

2. Results

2.1. Demographics and diagnosis (Table 1)

Twenty-nine children (15 boys, 14 girls) underwent surgery for HPT at our institution. Six children (3 boys, 3 girls) had neonatal severe hyperparathyroidism (NOSHPT) and presented in infancy [3 days–4 months (median 2 weeks)] and 23 children (12 boys, 11 girls) presented later in childhood with familial [7–6 years (median 13 years)] and sporadic HPT [8–16 years (median 15 years)]. Seven children had familial [4 MEN1, 1 MEN2a, 1 hyperparathyroidism jaw tumour syndrome, (HPT-JT) 1 X linked hypophosphataemia, XLHP] and sixteen sporadic HPT. The age at presentation, sex differences and the age at the time of surgery between children with familial and sporadic HPT were not significantly different [p = 0.64 (gender), p = 0.99 (age), p = 0.83 (age at operation)].

2.2. Clinical presentation

The symptoms involving gastrointestinal, renal, skeletal and neurological systems were not mutually exclusive.

Four neonates presented with gastrointestinal symptoms of poor feeding/vomiting and two with jaundice. Skeletal abnormalities were noted in three neonates, including one with multiple rib fractures, flail chest and respiratory failure requiring mechanical ventilation on the intensive care unit. Neurological symptoms identified in four neonates included developmental delay (3) and lethargy (2).

In the older group, gastrointestinal symptoms were the commonest presenting complaint affecting eight children and included abdominal pain (6), vomiting (3), constipation (2) and diarrhoea (1). Three children had skeletal abnormalities, one child had deformity of the knees and two had osteomalacia. Two children had acute renal colic owing to calculi and two children presented with CNS symptoms of depression with suicidal ideation (1) and lethargy (1), both in conjunction with gastrointestinal symptoms. Incidental diagnoses were made in two asymptomatic children; one child diagnosed on a preoperative blood test for a cochlear implant and the other child was investigated for premature adrenarche.

2.3. Biochemical and genetic findings

Calcium and PTH concentrations on presentation in the neonatal group ranged from 3.03–8.10 mmol/l (median 4.02 mmol/l) and from 15.8 to 360 pmol/l (median 56.9 pmol/l) respectively (Table 1). Four neonates tested positive for mutations of the CaSR gene encoding the calcium sensing receptor. Itwo neonates—2nd degree relatives: homozygous p.Q164X, one homozygous p.C570, one compound heterozygote p.R680C (paternal) and one p.C60F (maternal).

Older children had calcium and PTH concentrations ranging from 2.75 to 4.09 mmol/l (median 3.10 mmol/l) and from 9.4 to 62 pmol/l (median 16.4 pmol/l) respectively. Differences between serum calcium and PTH levels in children with the familial and sporadic HPT were not statistically significant [p = 0.80 (calcium), and p = 0.37 (PTH)].

2.4. Localisation studies

Ultrasonography was performed as a solitary investigation in two neonates and in combination with MIBI scanning in two; the remaining two patients did not have any imaging carried out. None of the scans identified abnormal glands.

In older children, ultrasonography was performed in 17 (14 sporadic and 3 familial HPT) and this was in conjunction with MIBI scanning in 16 children (13 sporadic and 3 familial HPT). The ability of US and MIBI imaging to distinguish solitary from multiple glands disease and to accurately predict the laterality of the abnormal solitary gland was 100%. In children with sporadic HPT, the accuracy of US and MIBI for precise quadrant localisation of abnormal gland

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<td>Demographics, calcium and PTH levels.</td>
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<td>Gender—M:F</td>
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<td>Age at diagnosis</td>
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<td>Age at operation</td>
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<tr>
<td>Calcium levels at diagnosis (mmol/l)</td>
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<tr>
<td>Normal: 2.15–2.74</td>
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<td>PTH levels at diagnosis (pmol/l)</td>
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<td>Normal: 1.1–5.4</td>
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* 4, MEN1, 1 MEN2a, 1 HPT-JT, 1 X linked H.
position was 96% for both modalities. The sensitivity and specificity of ultrasound were 93 and 98% respectively, and the sensitivity and specificity for MIBI scanning were 92 and 97% respectively. Findings of US and MIBI were concordant in all cases of solitary gland disease.

Only one out of four children with MEN1 had US and MIBI, which identified abnormal bilateral lower glands, but both imaging modalities missed the abnormal hyperplastic left upper parathyroid. The child with X linked HP had an inconclusive US, while MIBI demonstrated multigland enlargement. The child with HPT-JT had US and MIBI scanning which accurately localised a left lower parathyroid adenoma.

Parathyroid venous sampling (PVS) was the imaging modality used at our institution prior to 1980, and this was performed only in two children. Both children (1 sporadic HPT, 1 MEN2a), had single gland disease, which was confirmed by PVS.

3. Surgery, pathology and outcomes

3.1. Children with NSHPT

Children who failed to respond to medical treatment underwent surgery between 3 weeks to 3 years of age (median 5 months) (Table 2). Five of them had 4 and one had 3 ½ glands removed. Histology confirmed hyperplasia of all excised parathyroid glands in the five children who had 4 glands removed, but the histology for the sixth child who had a ¾ glands parathyroidectomy was reported as normal. Five children who had 4 glands removed developed prolonged postoperative hypocalcaemia owing to hungry bones syndrome and were aggressively treated with IV calcium infusion (2–9 days, median 6 days) followed by oral supplementation with calcium and α-calcidol. Post-operative follow up ranged from 4 months to 10 years (median 8 years). In the 5 children who had 4 glands removed, the PTH concentrations were undetectable and normal calcium [2.20–2.62 mmol/l (median 2.54 mmol/l)] concentrations were maintained with oral supplementation. The child who had the ¾ glands parathyroidectomy remained mildly hypercalcemic on short term follow-up and had an elevated parathyroid hormone concentration of 33.7 pmol/ml post operatively. Although this child was not cured as judged by biochemical criteria, she had no further surgery owing to lack of symptoms. She was successfully managed conservatively and after 10 years, her calcium and parathyroid concentrations were normal (2.60 mmol/l and 2.1 pmol/l respectively).

3.1.1. Older children with familial HPT

Three children with familial HPT (2 MEN1 and 1 with X linked HP) had 4 glands and four (2 MEN1, 1 MEN2a, 1 HPT-JT) had 3 glands removed. Histology in children with MEN1 showed that one child had hyperplasia of 4 glands, one child had 2 adenomas and 2 hyperplastic glands, one child had 3 glands hyperplasia and one child had 2 glands with nodular hyperplasia and 1 normal gland. The child with X linked HP had 4 hyperplastic glands, the child with MEN2a had 1 solitary adenoma and 2 normal glands and the child with HPT-JT had 1 solitary adenoma and 2 normal glands.

Children who had 4 glands removed were symptomatically hypocalcaemic postoperatively, stayed in hospital for 6 days and maintained normal calcium concentrations with oral (calcium, Calcidol) supplementation on follow up ranging from 4 to 12 years (median 5 years). Four children who had 3 glands removed had postoperative hypocalcaemia with 2 children requiring intravenous and 2 oral calcium replacement. The average length of stay for this group was 5 days. One child with MEN1 who had 3 glands removed required a reoperation owing to symptomatic hypercalcaemia 10 months after the initial procedure. Following the removal of the 4th gland, normal calcium concentrations were maintained without calcium supplementation. One child who had 3 glands removed has detectable PTH but remains on calcium and vitamin D supplementation 1 year after surgery and two children maintained normal calcium concentrations without supplementation at follow up of 4–10 years.

3.2. Older children with sporadic HPT

Parathyroid surgery performed in children with sporadic HPT reflects significant changes in the management of this disease in our institution over the last three decades. Prior to 1980, two children had bilateral neck explorations and 3 glands removed. Histology in both children confirmed a solitary adenoma with 2 normal glands. Between 1980 and 2002, five children underwent bilateral neck explorations, three of them had a single abnormal gland and one child had 1 abnormal parathyroid removed and 1 normal looking gland biopsied. Removed abnormal 4 glands were confirmed to be parathyroid adenomas and biopsied gland was normal on histology. The remaining child underwent a neck exploration and biopsies of the four glands, which were identified to be hyperplastic on histology. This was the only child in the group with sporadic HPT who had hyperplasia of all 4 glands. After 2002, nine children underwent minimally invasive parathyroidectomy and had a single gland removed in each case. In the last seven cases, intraoperative PTH measurements were used. Histology confirmed adenomas in all children.

Post operatively, three children developed transient symptomatic hypocalcaemia. One child required intravenous calcium replacement followed by oral supplementation and two had short term oral calcium supplementation. The average length of stay for this group was 3.1 days, and the average length of stay for the children who underwent minimally invasive parathyroidectomies was 2 days. During follow up which ranged from 2 months to 10 years (median 3 years), none of the children required reoperation and all had normal calcium levels ranging from 1.97 to 2.56 mmol/l (median 2.44 mmol/l).

None of the neonates with NSHPT or older children with familial and sporadic HPT who underwent parathyroidectomy had postoperative

![Table 2](image)

Surgical management of all children with hyperparathyroidism.

<table>
<thead>
<tr>
<th>Number of children</th>
<th>Neonates</th>
<th>Older children Sporadic</th>
<th>Older children Familial</th>
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<td>Total (4 gland)</td>
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<td>5</td>
<td>No reoperations</td>
<td>3</td>
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<td>Subtotal (3 gland)</td>
<td>1</td>
<td>Failure to normalise calcium and PTH but no reoperation</td>
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<td>parathyroidectomy</td>
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<td>1 reoperation for recurrence in MEN1 child</td>
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bleeding, infection or problems related to recurrent laryngeal nerve injury. There were no mortalities.

4. Discussion

The number of children who had surgery for hyperparathyroidism reported in the world literature is small, with the eight largest published studies describing a combined total of only 200 children [1–5,9,10]. Our case series contributes to the present knowledge of this rare condition by highlighting differences between HPT in children and adults and examining the impact of new technologies on their management.

First, our experience and the published reports from other large tertiary centres show that parathyroid surgery in children constitutes only 0.75 to 3% of parathyroid operations in adults performed during the same period [5,11,12]. The incidence (1 per 300,000 live births) and prevalence (2–5 per 100,000) of HPT in children and the incidence (20 per 100,000) and prevalence (1 in 1000) in adults suggest that in children this condition is at least 100 times less frequent [5,13,14]. Second, our series and the French series [5], both of which included neonates affected by NSHPT and older children, clearly show a bimodal age distribution, with an early peak during the neonatal period and a second peak from the age of 6 years to adolescence. Previously published series of children with HPT [2,4–6,10] included patients who were 18 years or even 30 years old and reported a predominant female to male ratio, similar to adults, where a strong female preponderance has been firmly established [10,11,15,16]. Only children up to 16 years of age, which is the cut off point for being considered a child in the UK, were included in our series demonstrating a slight male preponderance. This finding and the fact that only 2/23 older children in our series, 3/52 in the Mayo series [2] and 7/44 children in French series [5] were younger than 10, suggest that boys are affected as frequently as girls and that HPT is uncommon in younger children. Third, 46% of all cases and 32% of older children in our series had familial HPT, the highest incidence of genetically determined disease reported in the literature. High incidence of familial HPT in children is also well documented in the series from France (25%) [5], Mayo Clinic (31%) [2] and Wisconsin (24%) [6]. This is significantly higher than the rate of familial HPT in adults and the current UK guidelines recommend the routine genetic testing of all children presenting with HPT [17,18]. Positive genetic testing is important in establishing the diagnosis, planning treatment and initiating biochemical and genetic screening of siblings and parents. In neonates with NSHPT, certain CaSR mutations are associated with more severe disease and identifying the mutation can help select patients for either surgical or long term medical treatment. However, children with the same genotype could have a different clinical course and the decision to operate or treat conservatively is currently based more on high calcium and PTH levels and the development of life threatening complications than the type of mutation. In older children, testing for mutations should start with MEN11 followed by parafibrinomin gene if the former test is normal, 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 with MEN2a [17,18]. An alternative and a more selective approach would be to test all children with a positive family history, clinical features suggesting a genetic background and the presence of more than one abnormal parathyroid gland on pre-operative imaging. Children suspected of having sporadic HPT and radiologically confirmed solitary adenoma, can be scheduled for parathyroidectomy without further tests. This approach has been also recommended by Durkin [6]. Fourth, 90% of children in our series had symptoms affecting predominantly the gastrointestinal, skeletal and renal systems. Other reports also showed that the majority of children with HPT, in contrast to 80% of adults who are asymptomatic at presentation, had symptoms and end organ damage at the time of diagnosis [1,2,4–6]. These findings and the high levels of calcium and PTH at presentation suggest that HPT in children is diagnosed late. More frequent measurement of calcium and PTH in children with otherwise unexplained symptoms could lead to earlier diagnosis and less complications.

Imaging of abnormal parathyroid glands has a great influence on the choice of the most appropriate surgical approach in adults [7]. However, our study shows that neonates with NSHPT do not benefit from preoperative localisation studies as none of the abnormal glands were identified. Imaging with US and MIBI in older children with familial HPT was also of limited value. It is our view that in children with familial HPT, it is justified to proceed with surgery without preoperative imaging. Familial HPT is commonly caused by hyperplasia of multiple glands, which shows poorly on imaging. Localisation of abnormal glands in familial HPT is also not essential as the recommended operation is direct visualisation of all glands and the removal of abnormal glands. US and MIBI scanning is however very valuable in identifying position of the solitary abnormal glands in children with sporadic HPT. Both tests accurately predicted the laterality of the abnormal gland in all cases and interestingly US and MIBI findings were always concordant. Although our current policy is to perform US and MIBI on all children with sporadic HPT, it seems possible to simply rely on the US localisation and perform MIBI only in children with negative or inconclusive findings on US. This approach, if successful, would reduce the cost of investigations and prevent unnecessary dose of radiation, which in the case of MIBI is significant. Other imaging modalities such as CT, MRI and venous sampling with selective angiography should be reserved only for children with recurrent HPT who require a second operation.

Surgical removal of abnormal parathyroid glands is the best treatment in the majority of children diagnosed with HPT but the type of underlying pathology, presence of mutation, age and clinical condition of a child must be considered when choosing the timing and type of surgical approach.

There is growing evidence that, in some children with NSHPT, medical management can alleviate the need for surgery [5,19,20]. All neonates in our series were initially treated conservatively with a low calcium diet, rehydration, diuretics, bisphosphonates and recently with the calcimimetic agent, cinacalcet. Six children who did not respond to conservative management had surgery. Timing of operation varied from weeks to years and depended mainly on the impact of high calcium and PTH levels on child health. One neonate required lifesaving parathyroidectomy within weeks of being born because of the rapidly disappearing skeleton, fractured ribs with a flail chest necessitating intubation and ventilation on ITU. Other children, the oldest 3 years old, had parathyroidectomy because of difficulty in controlling very high calcium and PTH levels requiring multiple hospital admissions and intravenous medications, deterioration of bone mineralisation on skeletal survey and failure to thrive. The immediate effect of surgery and its main advantage over conservative management is the removal of the devastating effect of high PTH on the skeleton. This can be only achieved by performing a total parathyroidectomy and in our practice we always strived to remove all 4 glands. Subtotal or total parathyroidectomy with autografting of parathyroid tissue into the skeletal muscles is an option, but risks persistent or recurrent hyperparathyroidism. It is not clear from published evidence whether children who had total, subtotal parathyroidectomy or conservative management without parathyroidectomy have different long term outcomes. Follow up of children in our series who had a total parathyroidectomy demonstrated good calcium control with oral supplementation, none of the children required further operations and their development is progressing well. This is consistent with the literature, confirming the important role of surgery in this age group [5,9].

The timing and choice of the optimal operation in older children depend on the sporadic or familial nature of HPT. We are of the opinion that in older children with HPT, conservative management is almost never indicated. This is confirmed by our findings that all
children in this series had strong indications for surgery on the account of high calcium and symptoms or evidence of end organ damage. Bilateral neck exploration and direct intraoperative visualization of all parathyroids is the operation of choice in children with familial HPT. Preserving some of the parathyroid function, especially in younger children, by either removing 3½ glands or performing total parathyroidectomy with autografting of some parathyroid tissue into the muscle is an option. This approach can temporarily cure hyperparathyroidism and maintain normocalcaemia without calcium supplementation, but carries a high risk of recurrence. In our study, this was illustrated by the child with MEN1 who initially had 3 glands removed and required a further operation to remove the remaining gland owing to a recurrence of symptoms. Removing all four glands, in our hands, was always curative and children remain normocalcaemic with appropriate supplementation. Our study supports the use of minimally invasive parathyroidectomy in children with sporadic HPT. All nine recently operated children who had MIP were cured. We have also demonstrated by reviewing their histology that the six children operated before 2002 who had BNE would have also benefitted from MIP as all of them had single abnormal glands. Only one child with sporadic HPT had 4 gland hyperplasia and required BNE. Intraoperative PTH measurements, which we have used since 2005, are useful in children with sporadic HPT confirming immediate normalisation of PTH levels. Persistently raised PTH levels after removal of a gland will alert the surgeon to another source of PTH hypersecretion, and force a further search for abnormal glands. This approach is also supported by the findings of Durkin et al [6].

In our series none of the children had complications related to RLN injury, bleeding or infection. Excellent clinical outcomes were also demonstrated by other series [2,6]. Our study confirmed that parathyroidectomy in children of all ages can be performed safely with a minimal rate of perioperative complications. Centralisation of parathyroid surgery in children in the hands of a few experienced surgeons, who operate within institutions providing adequate facilities and multidisciplinary expertise, is an important factor in maintaining good results. Currently, a registration facility has been agreed with the Children’s Tumour Registry for children with HPT up to the age of 21 years including family members identified through screening. The aim of this facility is to identify and improve incidence and outcome measures.

We acknowledge the limitations of this study owing to the retrospective nature of the data collection. Selection bias is possible as we relied on medical coding to identify the children with HPT and the accuracy of the data collected was dependent on quality of medical records. Laboratory techniques for measurement of PTH levels have evolved over the time frame of this series and it was necessary to convert all PTH results to pmol/l.

In conclusion, HPT in children is rare, frequently familial and boys and girls are equally affected. It is often diagnosed late in children thereby presenting with high levels of calcium and PTH with most of them symptomatic at the time of diagnosis. Imaging is accurate in children with sporadic HPT but is of less value in familial disease caused by hyperplastic glands. All children with HPT should have genetic tests. We have demonstrated that parathyroid surgery in children of all ages is safe and good long term outcomes are achieved in the centres of excellence. Removal of multiple glands is necessary to cure children with familial HPT but minimally invasive parathyroidectomy is the operation of choice in children with sporadic HPT.

References