Primary hyperparathyroidism in a paediatric hospital

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Summary

We retrospectively reviewed the presentation and management of children with primary hyperparathyroidism (PHPT) from 1973 to 1995 at a paediatric tertiary-care centre. There were 11 patients (6 females), aged 12.3–17.7 years at presentation, with sporadic PHPT confirmed by histopathology (single adenoma). Presentation consisted of renal colic, or non-specific gastrointestinal, musculoskeletal or neurological symptoms. Misdiagnosis was common until hypercalcaemia was identified, 0.5–24 months after onset of symptoms (mean 7.7 months). All patients had hypercalcaemia and low-normal serum phosphate. The parathyroid hormone (PTH) radioimmunoassay used before 1986 was elevated in 1/4 patients; the intact PTH assay used after 1986 was elevated in 7/7 patients. At presentation, six had end-organ damage: band keratopathy, renal lesions, and/or bone disease. Preoperative localization was accurate in 0/4 patients diagnosed before 1986, but 5/7 patients diagnosed after 1986: three by ultrasound or sestamibi scan alone, and two by ultrasound and technetium scan. Surgical outcome was not dependent upon the accuracy of pre-operative localization. PHPT is rare in children but usually associated with end-organ damage, presumably due to delayed diagnosis. It should be considered in the differential diagnosis of unexplained non-specific complaints. The intact PTH assay greatly assists pre-operative diagnosis. The usefulness of pre-operative localization requires further research.

Introduction

Primary hyperparathyroidism is a rare disease in children and adolescents.1,2 It was reviewed in 1982 in two separate papers describing 103 cases reported worldwide,3,4 with an additional seven patients reported in a 1986 review.5 Several case reports have been described since.6–10 These reports emphasize that establishing the diagnosis of PHPT is difficult in children, and often delayed because of the non-specific presenting symptoms. In addition, because the disease is rare, paediatricians often fail to consider PHPT, and thus fail to measure serum calcium when they are investigating unexplained non-specific complaints.

In previous years, the measurement of serum calcium was often imprecise and the available PTH assays lacked both sensitivity and precision.11 Preoperative localization using available imaging techniques was difficult to perform and was inaccurate. Since the last series was published, there have been significant advances which have facilitated the diagnosis of PHPT: (i) the accuracy of serum calcium measurement has improved significantly; (ii) sensitive two-site PTH assays that accurately measure only the intact, active form of PTH are now available;12 and, (iii) the use of new or improved imaging modalities for pre-operative localization including real-time ultrasound, parathyroid scintigraphy, high-resolution CT and MRI. In light of these advances in PTH assays and imaging modalities, we reviewed our experience with PHPT over the last 22 years at the Hospital for Sick Children, Toronto.

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Methods

Patients were eligible for inclusion in this study if they were aged <19 years and had been diagnosed with primary hyperparathyroidism between January 1 1973 and December 31 1994. Medical records at HSC were searched for all diagnoses of PHPT made among patients as a result of in-patient or out-patient care, death certificate or autopsy. Our search identified eleven patients diagnosed with primary hyperparathyroidism over this 22-year period. Two additional patients who were neonates at the time of diagnosis were excluded, because neonatal PHPT is a different disease.

All patients were referred to the Pediatric Endocrinology Service for investigation of hypercalcaemia. The diagnosis of PHPT was made on the basis of hypercalcaemia, normal-to-low serum phosphate, and elevated or non-suppressed serum parathyroid hormone concentrations. Four patients were diagnosed before the availability of sensitive PTH assays and therefore, diagnosis required additional investigations including cortisone suppression tests and selective venous sampling for PTH. Diagnosis was confirmed by pathological specimens obtained through surgical exploration of the neck (ten patients) or mediastinum (one patient).

Medical records were reviewed in detail to determine clinical presentation, biochemical findings, imaging studies, pre-operative course, surgical and pathological data, and post-operative course. Follow-up data were obtained from chart records with confirmation by telephone, except for three patients who were lost to follow-up, 1, 2 and 5 years post-operatively.

Biochemistry

The Kodak Ektachem Analyzer was used for serum calcium and phosphate after 1983 and alkaline phosphatase after 1985. Earlier analyses were performed on Electro-Nucleonics Industries Gemsaec (alkaline phosphatase) and Technicon AutoAnalyzer I, Greiner Selective Analyzer II methodologies (calcium, phosphate). Ionized calcium was measured by Radiometer ICA or Nova Stat Profile 4. Results were interpreted according to appropriate age-specific reference values. Before 1986, PTH was measured in the laboratory of Dr T.M. Murray at St. Michael’s Hospital, Toronto, with a radioimmunoassay using an antibody raised in guinea pigs to both C- and N-terminal sequences of PTH.11 After 1987, 'intact PTH' kits were used from Nichols Institute Diagnostics, San Juan Capistrano, CA.12

Imaging

The original radiographic studies and reports for nine of the patients were reviewed. The films obtained on two patients early in the study period had been destroyed, so only the reports were reviewed.

Results

Patient characteristics

Eleven patients (6 females, 5 males) were diagnosed with PHPT between 1973 and 1993. Four were diagnosed before and seven after 1986 (when we started using the more sensitive, two-site PTH assay).

Age at presentation was 12.3–17.7 years (Table 1).

Patient 1 was known to have Riley-Day Syndrome (Familial Dysautonomia). Between the ages of 8 and 17 years, she had over 30 hospital admissions for intractable vomiting. These attacks were attributed to recurrent aspiration pneumonia, a common complication of Riley-Day Syndrome. Hypercalcaemia (3.75 mmol/l or 15 mg/dl) was identified as a potential cause at age 17 years; chart review revealed that hypercalcaemia had been documented 2 years previously. The vomiting episodes ceased following surgical removal of a parathyroid adenoma.

A 12 year old boy (patient 2) with a four-year history of deteriorating school performance presented to the rheumatology service with a one-month history of arthritis of both knees, and was subsequently found to have hypercalcaemia (4.20 mmol/l or 16.8 mg/dl). X-rays were normal. Bone biopsy was consistent with primary hyperparathyroidism. Joint fluid was not examined. Five patients (3,4,5,7,11) presented with typical renal colic and stones. Hypercalcaemia was identified in the course of investigating the aetiology of the stones.

A 14-year-old girl (patient 6) presented with an eight-week history of recurrent vomiting and abdominal pain. An abdominal ultrasound revealed mild increased echogenicity of the gall bladder, and a cholecystectomy was performed. The gall bladder pathology was negative but her symptoms subsided. Two months later, the vomiting recurred, and further investigations revealed hypercalcaemia (4.54 mmol/l or 18.18 mg/dl).

Patient 8 presented with refractory hypertension at 17.5 years. Investigations during an annual physical examination 2.5 years previously had identified nephrotic-range proteinuria and elevated serum creatinine (92 µmol/l or 1.04 mg/dl) which worsened over the next 6 months. Serum calcium was 2.61–2.67 mmol/l (10.44–10.68 mg/dl), phosphate 0.85–1.16 mmol/l (2.63–3.59 mg/dl) and alkaline phosphatase 121 U/l. Renal ultrasound was normal. Renal biopsy was inconclusive, and a presumptive diagnosis of membranous nephropathy or focal segmental glomerulonephritis was made. Renal function was stable over the next 2 years without requiring...
Primary hyperparathyroidism

Table 1  Clinical presentation and outcome

<table>
<thead>
<tr>
<th>Patient</th>
<th>Date seen</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Clinical presentation</th>
<th>Duration of symptoms (months)</th>
<th>Location of lesion</th>
<th>Size of lesion (cm²)</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3/73</td>
<td>F</td>
<td>17.5</td>
<td>Vomiting (Riley-Day Syndrome)</td>
<td>24*</td>
<td>neck</td>
<td>?</td>
<td>Adenoma</td>
</tr>
<tr>
<td>2</td>
<td>5/76</td>
<td>M</td>
<td>12.3</td>
<td>Arthritis (school difficulties)</td>
<td>1.0 (48.0)</td>
<td>neck</td>
<td>0.135</td>
<td>Adenoma</td>
</tr>
<tr>
<td>3</td>
<td>5/80</td>
<td>M</td>
<td>15.2</td>
<td>Renal colic</td>
<td>2.5</td>
<td>neck</td>
<td>0.160</td>
<td>Adenoma</td>
</tr>
<tr>
<td>4</td>
<td>6/81</td>
<td>M</td>
<td>12.3</td>
<td>Renal colic (Klinefelter's)</td>
<td>1.5</td>
<td>neck</td>
<td>0.495</td>
<td>Adenoma</td>
</tr>
<tr>
<td>5</td>
<td>8/87</td>
<td>M</td>
<td>15.0</td>
<td>Renal colic</td>
<td>0.5</td>
<td>mediastinum</td>
<td>0.375</td>
<td>Adenoma</td>
</tr>
<tr>
<td>6</td>
<td>12/89</td>
<td>F</td>
<td>14.3</td>
<td>Vomiting Cholecystectomy</td>
<td>4.0</td>
<td>neck</td>
<td>1.500</td>
<td>Adenoma</td>
</tr>
<tr>
<td>7</td>
<td>5/90</td>
<td>F</td>
<td>16.7</td>
<td>Renal colic</td>
<td>11</td>
<td>neck</td>
<td>1.260</td>
<td>Adenoma</td>
</tr>
<tr>
<td>8</td>
<td>9/92</td>
<td>F</td>
<td>17.5</td>
<td>Hypertension</td>
<td>14</td>
<td>neck</td>
<td>3.960</td>
<td>Adenoma</td>
</tr>
<tr>
<td>9</td>
<td>10/92</td>
<td>F</td>
<td>13.0</td>
<td>Asymptomatic (learning difficulties)</td>
<td>n/a</td>
<td>neck</td>
<td>1.386</td>
<td>Adenoma</td>
</tr>
<tr>
<td>10</td>
<td>12/92</td>
<td>F</td>
<td>15.0</td>
<td>Muscle weakness</td>
<td>13</td>
<td>neck</td>
<td>5.76</td>
<td>Adenoma</td>
</tr>
<tr>
<td>11</td>
<td>11/94</td>
<td>M</td>
<td>17.7</td>
<td>Renal colic</td>
<td>5</td>
<td>neck</td>
<td>0.18</td>
<td>Adenoma</td>
</tr>
</tbody>
</table>

*Vomiting was present from ages 8–17.5 years; hypercalcaemia was first noticed at 15.5 years but may have been present longer.

medications until she presented with hypertension and progressive renal insufficiency (serum creatinine 1304 μmol/l or 14.7 mg/dl). She then had evidence of both primary and secondary hyperparathyroidism (serum calcium 3.12 mmol/l or 12.5 mg/dl, serum phosphate 2.69 mmol/l or 8.33 mg/dl, PTH 777 ng/l).

A 13 year old girl (patient 9) was found to be hypercalcaemic (3.16 mmol/l or 12.6 mg/dl) through routine blood work at the time of an annual physical examination by her family doctor. She was known to have a learning disability but was otherwise asymptomatic.

Patient 10 presented to the neurology service at 14 years of age with muscle cramps and difficulty walking. She was noted to have proximal muscle weakness and the diagnosis of polymyositis was considered. Electromyography and nerve conduction studies were consistent with a myopathic process, but serum creatine kinase and muscle biopsy were normal. The muscle weakness worsened, as did her walking, with increasing genu-valgum deformity. A year after the symptoms began, her serum calcium was found to be elevated (3.03 mmol/l or 12.1 mg/dl). By this time, she had developed bilateral slipped capital femoral epiphyses.

Symptoms were present from 2 weeks to 24 months (mean 7.2 months) prior to identification of hypercalcaemia as a possible cause of our patients' symptoms. Three patients (1,8,10) had documented hypercalcaemia for 6 to 24 months before the link with their presenting symptoms was recognized or follow-up investigations arranged. Five of our patients had additional non-specific signs and symptoms including, in decreasing order of frequency: vomiting, anorexia, weight loss, polydipsia, arthralgia, non-renal abdominal pain, nausea, fatigue, muscle weakness, bone pain, constipation, and behaviour change.

Parents of two of the patients had histories of renal stones, but normal serum calcium excluded familial causes of hypercalcaemia. A third patient’s paternal grandmother had a parathyroidectomy for a ‘tumour’ at 48 years of age. The other eight patients had negative family histories.

End-organ effects (Table 2)

Hyperparathyroidism may cause damage to the eyes, kidneys and skeletal system. A slit-lamp examination was performed by an ophthalmologist on six patients. Band keratopathy (opaque material in parallel lines within the limbus of the eye, representing calcium deposition in the cornea) was noted in two of these patients.

Plain films of the abdomen, obtained alone or as part of an intravenous pyelogram, and/or renal ultrasounds were performed on all 11 patients. Two patients had evidence of nephrocalcinosis, although neither of these patients had renal stones. Five additional patients had renal calculi, four of whom had presented with renal colic, bringing the total number with kidney damage to seven patients.
Table 2  End-organ effects

<table>
<thead>
<tr>
<th>Patient</th>
<th>Skeletal X-rays</th>
<th>Bone scan</th>
<th>Abdominal X-rays</th>
<th>Renal ultrasound</th>
<th>Eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Subperiosteal resorption, hand</td>
<td>NA</td>
<td>Nephrocalcinosis</td>
<td>NA</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>Subperiosteal resorption, hand</td>
<td>Normal</td>
<td>Normal</td>
<td>NA</td>
<td>Band keratopathy</td>
</tr>
<tr>
<td>3</td>
<td>Normal</td>
<td>NA</td>
<td>Normal</td>
<td>NA</td>
<td>Bilateral nephrocalcinosis</td>
</tr>
<tr>
<td>4</td>
<td>Subperiosteal resorption, hand</td>
<td>NA</td>
<td>Left nephrolithiasis</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>5</td>
<td>Osteopenia</td>
<td>NA</td>
<td>Bilateral nephrocalcinosis</td>
<td>NA</td>
<td>Normal</td>
</tr>
<tr>
<td>6</td>
<td>Subperiosteal resorption, hand</td>
<td>Increased renal and skeletal activity</td>
<td>NA</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>7</td>
<td>Subperiosteal resorption, hand</td>
<td>NA</td>
<td>Bilateral nephrocalcinosis</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>8</td>
<td>Normal</td>
<td>Increased renal, skeletal and pulmonary activity</td>
<td>NA</td>
<td>Small, hyperchoic kidneys</td>
<td>Band keratopathy</td>
</tr>
<tr>
<td>9</td>
<td>Normal</td>
<td>NA</td>
<td>NA</td>
<td>Normal</td>
<td>NA</td>
</tr>
<tr>
<td>10</td>
<td>Pronounced osteopenia</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>11</td>
<td>Pronounced subperiosteal resorption</td>
<td>Bilateral nephrocalcinosis</td>
<td>NA</td>
<td>Normal</td>
<td>NA</td>
</tr>
</tbody>
</table>

8/11 had skeletal lesions on X-ray and/or bone scan; 7/11 had renal lesions on X-ray and/or ultrasound (does not include patient 8); 2/6 of those examined by slit lamp had band keratopathy.

NA, not attempted; SCFE, slipped capital femoral epiphyses.

Table 3  Biochemical findings

<table>
<thead>
<tr>
<th>Patient</th>
<th>Calcium (mmol/l)</th>
<th>Ion. Ca (mmol/l)</th>
<th>Phosphate (mmol/l)</th>
<th>ALP (U/l)</th>
<th>PTH (ng/l)</th>
<th>1,25(OH)2D (pmol/l)</th>
<th>25(OH)D (nmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal range</td>
<td>2.25–2.62</td>
<td>1.15–1.20</td>
<td>0.87–1.71</td>
<td>100–600</td>
<td>10–65</td>
<td>25–120</td>
<td>29–80</td>
</tr>
<tr>
<td>1</td>
<td>3.75</td>
<td>–</td>
<td>0.94</td>
<td>85</td>
<td>* 0.24</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>4.2</td>
<td>–</td>
<td>0.84</td>
<td>20</td>
<td>* 0.46</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>3.2</td>
<td>–</td>
<td>1.13</td>
<td>201</td>
<td>* 0.18</td>
<td>–</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>3.4</td>
<td>1.62</td>
<td>1.03</td>
<td>284</td>
<td>* 0.16</td>
<td>–</td>
<td>48</td>
</tr>
<tr>
<td>5</td>
<td>2.93</td>
<td>1.50</td>
<td>0.96</td>
<td>363</td>
<td>79</td>
<td>169</td>
<td>57</td>
</tr>
<tr>
<td>6</td>
<td>4.54</td>
<td>2.24</td>
<td>1.14</td>
<td>175</td>
<td>581</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>2.8</td>
<td>1.53</td>
<td>0.96</td>
<td>151</td>
<td>117</td>
<td>267</td>
<td>46</td>
</tr>
<tr>
<td>8 (initial)</td>
<td>2.64</td>
<td>–</td>
<td>1.00</td>
<td>121</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>(2 years later)</td>
<td>3.13</td>
<td>–</td>
<td>2.69</td>
<td>106</td>
<td>757</td>
<td>44</td>
<td>98</td>
</tr>
<tr>
<td>9</td>
<td>3.16</td>
<td>1.58</td>
<td>0.7</td>
<td>172</td>
<td>109</td>
<td>222</td>
<td>51</td>
</tr>
<tr>
<td>10</td>
<td>3.03</td>
<td>1.63</td>
<td>1</td>
<td>1735</td>
<td>930</td>
<td>272</td>
<td>18</td>
</tr>
<tr>
<td>11</td>
<td>3.14</td>
<td>1.55</td>
<td>0.91</td>
<td>151</td>
<td>159</td>
<td>126</td>
<td>54</td>
</tr>
<tr>
<td>Mean</td>
<td>3.39</td>
<td>1.66</td>
<td>1.12</td>
<td>313</td>
<td>NA</td>
<td>184</td>
<td>57</td>
</tr>
</tbody>
</table>

* PTH by RIA (ng/ml); normal < 0.3 ng/ml.

Plain radiographs of the skeleton were obtained on all eleven patients; three of these patients also had bone scintigraphy. Eight patients had radiographic evidence of hyperparathyroidism on skeletal X-rays or bone scans. The classic plain-film finding of subperiosteal resorption involving the radial aspect of the second middle phalanx of the hand was seen in six patients (Figure 1). Osteopenia, characterized
Figure 1. Patient 9: classic plain-film findings in PHPT of subperiosteal resorption involving the radial aspect of the second middle phalanx (large arrow) and the distal tufts (small arrow).

as a generalized osseous rarefaction with accentuation of the bony trabeculae, was mild in three patients and severe in one. Our most severely affected patient also demonstrated other classic radiographic findings of PHPT: pronounced subperiosteal resorption along the proximal medial tibiae and distal medial femora; subligamentous resorption along the distal clavicles and greater trochanters; subchondral resorption affecting the pubic symphysis, radioulnar joints, and sacroiliac joints; marked resorption of the digital tufts and lamina dura; severe osteopenia of the calvarium, vertebral column, and pelvis; and bilateral slipped capital femoral epiphyses (SCFE) (Figure 2). Bone ages in all patients were within the normal range. No brown tumours were seen. Aside from our profoundly affected patient with bilateral SCFE, no pathological fractures were observed.

The bone scans were consistent with the skeletal changes on plain films in only one of the three patients who had both studies. In one patient with positive plain films, the bone scan was normal; in a second patient (patient 6) both the plain films and bone scan were abnormal, the latter showing abnormal osseous activity and increased tracer uptake in the lungs and stomach, felt to represent metastatic microcalcification; a third patient (patient 8) demonstrated numerous, symmetrical foci of increased osseous activity and increased activity in the kidneys on the bone scan, but the plain films were normal.

Overall, ten out of eleven patients had evidence of organ damage at the time of presentation; two had band keratopathy, seven had nephrocalcinosis or renal calculi, and eight had evidence of bone disease. Only the asymptomatic patient was free of organ effects.

Biochemical findings

All patients had hypercalcaemia on initial presentation confirmed by subsequent measurements (Table 3). Mean total calcium was 3.39 mmol/l (13.56 mg/dl). Ionized calcium was also elevated in the seven patients in whom it was measured (1.50–2.24 mmol/l or 6.0–8.96 mg/dl) and correlated with total calcium values \( r = 0.97 \). Serum phosphate was low or normal in all patients except the patient with both primary and secondary hyperparathyroidism in whom it was elevated (2.69 mmol/l or 8.33 mg/dl) as expected because of renal failure. Alkaline phosphatase was normal in all patients, except the patient who presented with muscle weakness and evidence of severe bone disease (alkaline phosphatase 1735 U/l). Serum 1,25(OH)\(_2\)D was measured in six patients and was elevated except in the patient with renal failure. Serum 25(OH)D was normal in six patients. Patient 8, who had primary renal failure had a slightly elevated 25(OH)D, possibly due to recent increased sun exposure in Nigeria; patient 10, who had severe bone disease and the highest PTH at presentation, had a low 25(OH)D which may have been due to infrequent exposure to sunlight and low intake of milk. The low level may also have been aggravated by increased conversion to 1,25(OH)\(_2\) as a result of high PTH.

Random PTH levels were elevated in only one of the four patients diagnosed early in the study period when the single-site assay was used. However, none of these patients had suppressed PTH levels in the presence of hypercalcaemia, thereby supporting the diagnosis of PHPT. All seven patients diagnosed later when the two-site PTH assay was in use had elevated PTH assays (79–930 ng/l, normal 10–65 ng/l).

Pre-operative localization (Table 4)

Studies performed to localize the responsible parathyroid lesion varied during the twenty-two years of
Figure 2. X-ray of pelvis (patient 9) shows pronounced osteopenia and bilateral slipped capital femoral epiphyses (arrows).

Figure 2. X-ray of pelvis (patient 9) shows pronounced osteopenia and bilateral slipped capital femoral epiphyses (arrows).

our study and reflected the available imaging technology. Localizing procedures included selective venous parathyroid hormone sampling, angiography, neck ultrasonography, parathyroid scintigraphy, and computed tomography and magnetic resonance imaging of the neck and mediastinum.

In the four patients diagnosed between 1973 and 1986, attempts at pre-operative localization were made on three patients, and all were unsuccessful. Each of these patients had selective venous sampling and PTH assays using the less sensitive radioimmunoassay method. These studies were consistent with primary hyperparathyroidism but were unable to localize the lesion. One of these patients also had both a neck ultrasound and CT scan that were falsely negative. Parathyroid angiography was subsequently done and falsely identified a lesion on the opposite side to the true lesion. Following the angiography, the patient had a transient ischaemic attack resulting in hemiparesis, although he made a complete recovery within 24 h.

Pre-operative localization was attempted in all seven patients who presented between 1986 and 1994. Five of these seven patients had successful pre-operative localization. In three of the patients, the first and only imaging study accurately identified a single lesion—two by ultrasound (patients 6,10) and one by sestamibi scan (patient 11). In two additional patients, the neck ultrasound was either negative (patient 7) or showed bilateral lesions (patient 8). Subsequent technetium scans accurately identified single parathyroid lesions in both patients. In patient 9, bilateral lesions were seen on neck ultrasound and MRI, while a technetium scan was technically suboptimal and inconclusive. Neck exploration identified a single parathyroid lesion. Patient 5 was thought to have a unilateral lesion behind the right thyroid lobe based on an ultrasound study, but no pathology was found during neck exploration. He remained hypercalcaemic post-operatively. A second neck ultrasound was negative, as were CT and MRI of the neck and chest. Technetium scan was technically suboptimal. Selective venous sampling was subsequently performed and PTH measured using the sensitive, two-site intact PTH assay. Mediastinal PTH was six-fold higher than systemic levels. During surgical exploration, a parathyroid adenoma was removed from the thymus in the superior mediastinum.

Thus, in these patients diagnosed after 1986, pre-operative localization was inaccurate when imaging studies were reported as normal or showing bilateral lesions. But the identification of a unilateral neck lesion by ultrasound, technetium or sestamibi scan was accurate in five out of six patients with this finding. The only false-positive unilateral neck lesion was in the patient with the mediastinal parathyroid adenoma.

Surgery, pathology and post-operative course

Nine patients were operated on at The Hospital for Sick Children while two patients had the surgery performed elsewhere. A pathologist was on standby for frozen sections during each operation. Ten of the
patients had isolated parathyroid adenomas while one had an ectopic parathyroid adenoma located in the thymus. Pathological findings are shown in Table 1. Following removal of the parathyroid adenoma, at least one other gland was biopsied in each case to rule out the possibility of parathyroid hyperplasia. The normal glands were extremely small in all cases. The adenomas ranged in volume from 0.135 to 5.760 cm$^3$. The volume of the lesions was directly proportional to the duration of symptoms ($r = 0.84$). There was also a positive correlation between the PTH level and the volume of the lesion ($r = 0.92$). Postoperatively, one patient had mild hoarseness which resolved by 24 h. There were no other surgical complications and surgical outcome was unrelated to the accuracy of pre-operative localization. Seven patients became hypocalcaemic post-operatively; four of these patients became symptomatic, requiring treatment with combinations of oral calcium, vitamin D preparations and/or intravenous calcium infusion. Serum calcium normalized in five of these patients within 3 days, while patient 10 developed ‘hungry bone disease’ and was dependent on intravenous calcium infusion for 10 days. Patient 11 is now six months post surgery and remains on calcitriol. Post-operative PTH was normal in all patients, with follow-up ranging from 6 months to thirteen years (mean 4.5 years). Patient 8 has had

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### Table 4 Preoperative localization

<table>
<thead>
<tr>
<th>Patient</th>
<th>Neck ultrasound</th>
<th>Technetium scan</th>
<th>Sestamibis scan</th>
<th>CT</th>
<th>MRI</th>
<th>Angiography</th>
<th>Venography</th>
<th>Surgical findings</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Inconclusive (one-site assay)</td>
<td>Rt inferior PT adenoma</td>
</tr>
<tr>
<td>2</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Inconclusive (one-site assay)</td>
<td>Rt superior PT adenoma</td>
</tr>
<tr>
<td>3</td>
<td>Normal FN</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Left inferior parathyroid mass FP</td>
<td>Inconclusive (one-site assay)</td>
<td>Rt superior PT adenoma</td>
</tr>
<tr>
<td>4</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Rt superior PT adenoma</td>
</tr>
<tr>
<td>5</td>
<td>1 Mass right lobe of thyroid FP 2 (Post neck exploration)—normal TN Left inferior parathyroid nodule TP</td>
<td>Technically suboptimal</td>
<td>normal (neck/chest)</td>
<td>normal FN</td>
<td>NA</td>
<td>NA</td>
<td>Mediastinal TP (two-site assay)</td>
<td>Mediastinal PT adenoma</td>
</tr>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Lt inferior PT adenoma</td>
</tr>
<tr>
<td>7</td>
<td>Normal FN</td>
<td>Increased uptake on right TP</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Rt superior PT adenoma</td>
</tr>
<tr>
<td>8</td>
<td>Bilateral nodules TP/FP (true lesion unilateral)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Lt inferior PT adenoma</td>
</tr>
<tr>
<td>9</td>
<td>Bilateral nodules TP/FP (true lesion unilateral)</td>
<td>Technically suboptimal</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Bilateral lesions TP/FP (true lesion unilateral)</td>
<td>NA</td>
<td>Rt inferior PT adenoma</td>
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<tr>
<td>10</td>
<td>Left inferior parathyroid nodule TP</td>
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<td>NA</td>
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<td>NA</td>
<td>NA</td>
<td>Lt inferior PT adenoma</td>
</tr>
<tr>
<td>11</td>
<td>NA</td>
<td>Left inferior lesion TP</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Lt inferior PT adenoma</td>
</tr>
</tbody>
</table>

NA, not attempted; TP, true positive; TN, true negative; FP, false positive; FN, false negative.
progressive renal failure and now receives dialysis. Three of the patients presenting with renal colic had further episodes post-operatively until the stones were removed by lithotripsy. Patient 10 had surgical repair of the bilateral SCFE after her PTH and serum calcium levels had normalized. The other patients have had no recurrences of symptoms, including the child who presented with arthritis.

Discussion
Clinical presentation
PHPT remains an uncommon condition in children and adolescents. The Hospital for Sick Children is a tertiary-care centre for paediatric care with a referral base of approximately two million. During the study period, the hospital had approximately 25 000 admissions and 250 000 out-patient visits per year. Despite this large patient base, we were able to identify only 11 cases of primary hyperparathyroidism over a 22-year period, which is less than the reported prevalence of 2–5 per 100 000.13

PHPT affects 1:1000 adults, with 50–80% of these cases being identified while asymptomatic, through multiphasic screening biochemical profiles.14 Only one of our patients had asymptomatic PHPT, with no evidence of end-organ damage. Allen et al.7 reported a similar case in an 11-year-old boy. The prevalence of asymptomatic PHPT in children is not known, because routine biochemical profiles, including serum calcium determinations, are rarely done in healthy children and adolescents. It is certainly possible that there are children with asymptomatic PHPT within our catchment area who have yet to be identified. There is, however, no evidence that treatment of asymptomatic children is indicated, although there exists the potential for developing organ damage and growth disturbances as a result of decreased bone mineralization.7

The presentation of symptomatic PHPT in children has been well described.1,6 The majority of patients present in adolescence, accounting for 74–88% of cases. Our youngest patient was 12 years old when symptoms began. Although PHPT is 2–3 times more common in adult women than men,14 some paediatric series1,4 have found a higher prevalence in boys while others,2,3,5 including this series, have found no sex difference.

The clinical presentation of PHPT in adults has changed significantly over the past 40 years due to earlier diagnosis through better recognition and asymptomatic screening. Kidney stones used to account for 30–60% of adult presentations and symptoms from bone disease accounted for 10–20% of patients.15,16 However, a recent review found that only 20% of adults presented with kidney stones and 2% with skeletal disease, with the majority of adults being diagnosed while asymptomatic.17 The early reviews of PHPT in children found that most children present with non-specific complaints such as fatigue, weakness and weight loss.1-5 Five of our patients presented with renal colic, two with bone disease (arthritis and difficulty walking), two with recurrent vomiting, and one with hypertension; only one was asymptomatic. However, upon further questioning, five of our patients were also significantly bothered by non-specific complaints including anorexia, weight loss, fatigue, headaches, constipation, behavioural change and deteriorating school performance. The patients who presented with non-renal symptoms had a longer duration of symptoms prior to diagnosis of PHPT (range 1–24 months, mean 11.2 months), suggesting that their disease was less easily recognized than in those with renal symptoms (duration range 0.5–11 months, mean 4.1 months).

Diagnosis
In the past, PHPT was difficult to diagnose even when suspected. The first step is the establishment of hypercalcaemia, which is always present in PHPT, at least intermittently, and is due to the action of PTH increasing calcium transport from the gut and bone. However, hypercalcaemia presents a large differential diagnosis including familial hypocalciuric hypercalcaemia, vitamin D intoxication, immobilization, malignancy, and causes associated with renal failure. All of our patients had hypercalcaemia, although two were only marginally elevated at 2.80 and 2.93 mmol/l (11.2 and 11.82 mg/dl). Serum phosphate is usually low in PHPT as a direct result of PTH action on the kidney but it may be normal, as was the case with eight of our patients, and therefore a normal phosphate does not exclude the diagnosis of PHPT. Serum phosphate is not elevated in PHPT except in the presence of renal insufficiency as seen in patient 8.

The diagnosis of PHPT depends on the establishment of elevated serum PTH in the presence of hypercalcaemia. Until recently, PTH was difficult to measure accurately because circulating levels are normally very low (picomolar concentrations), and the previously used radioimmunoassays had low sensitivity and cross-reacted with circulating fragments from the parathyroid glands and peripheral metabolism, which accumulate in renal disease.11 The result was a high rate of both false positives and false negatives. The development of immunometric (also called two-site, sandwich or IRMA) PTH assays in the 1980s provided a very sensitive and specific assay which was able to distinguish the active form of PTH from the inactive fragments.12 Four of our
patients presented before the development of the immunometric assay. Although surgical pathology ultimately identified PHPT as the cause of their hypercalcaemia, none of them had elevated PTH, thus preventing a definite pre-operative diagnosis. All seven patients whose PTH was measured using the immunometric assay had elevated PTH, confirming PHPT as the cause of their hypercalcaemia.

In the presence of hypercalcaemia, low to normal serum phosphate, and an elevated PTH by immunometric assay, no further testing is required to make the diagnosis of PHPT. Other tests are frequently firming PHPT as the cause of their hypercalcaemia. Consequently, preventing a definite pre-operative diagnosis. However, the normal range for serum alkaline phosphatase, vitamin D metabolites, and urinary calcium excretion, although these additional tests are not necessary.

In adults with PHPT, an elevated serum alkaline phosphatase is believed to be a good marker of bone disease.18 However, the normal range for serum alkaline phosphatase in children (100–600 U/l) is much wider and more age-dependent than in adults (< 100 U/l), making this test less sensitive in the paediatric population. Of our patients, only patient 10, who had the most significant bone disease, had an elevated serum alkaline phosphatase.

25-Hydroxyvitamin D is usually in the low normal range in patients with PHPT,14 although we did not observe this except in the patient with severe bone disease. 1,25-Dihydroxyvitamin D is often elevated as a result of PTH stimulating production of this metabolite by the kidney; this effect was observed in five of six patients in whom it was measured and was low-normal as expected in our patient with renal insufficiency.

Hypercalciuria is commonly seen in PHPT because of increased load of calcium to the kidneys. However, hypercalciuria is less in PHPT than in hypercalcaemia due to non-parathyroid causes, because PTH stimulates reabsorption of calcium from the renal tubule.19 Unless urinary calcium is low, which strongly suggests familial hypocalciuric hypercalcaemia as the cause, measurement of urinary calcium excretion is unlikely to aid the diagnosis.

End-organ damage

Nephrolithiasis and nephrocalcinosis have been reported in 25–70% of children and adolescents with PHPT.1,2 Early studies suggested that renal disease was less common in children with PHPT than in adults.1,2,3 However, the prevalence of renal lithiasis or nephrocalcinosis in adults has declined in recent years as the proportion of asymptomatic patients has increased with the introduction of hypercalcaemia screening. In reports from the 1960s and 1970s, 40–80% of adult patients with PHPT had renal stones and/or nephrocalcinosis.14-16 More recent reviews found prevalences of 20–30%.17 We found renal stones or nephrocalcinosis in 7/11 patients. This suggests that the paediatric presentation is paralleling that of adults seen before the advent of hypercalcaemia screening.

Skeletal changes, consisting of subperiosteal resorption, osteopenia, kyphosis, resorption of the digital tufts and lamina dura, slipped capital femoral epiphyses, pathological fractures, and brown tumours, are reported to occur in 6–70% of cases of hyperparathyroidism in children and adolescents.1-6 The largest collective series of hyperparathyroidism in children, reported by Bjernulf and colleagues,1 contained 37 patients between the ages of 7 and 15 years, 23 of whom (62%) had demonstrable skeletal changes on plain films. The findings in our series are consistent with this data, with seven of eleven patients having abnormal skeletal X-rays, and one additional patient showing increased skeletal activity on bone scan. Other series have reported a lower incidence of bony changes, including that of Allo and colleagues4 in which only 6% of hyperparathyroid patients, aged 0–30 years, had skeletal abnormalities. Skeletal changes are reported to occur in 2–10% of adult hyperparathyroid patients.17

Only 20% of adult patients with primary hyperparathyroidism will demonstrate abnormalities on bone scintigraphy, such as increased uptake in the calvaria, mandible, sternum, acromioclavicular joints, sacroiliac joints, vertebral column, and along the shafts of the long bones.19 We are unaware of published paediatric series regarding skeletal scintigraphy findings in children with PHPT. Only three of our patients had bone scans performed; two of these scans were abnormal.

Previous reviews of PHPT in children and adults have not commented on the prevalence of band keratopathy. It is usually asymptomatic and therefore will not be identified unless the eyes are examined by slit lamp. Only six of our patients had ophthalmological examinations and band keratopathy was present in two of these patients.

Preoperative localization

There are few radiological studies of hyperparathyroidism in children. Available information is limited to isolated case reports.6,7,21-23 However, there is an extensive literature regarding parathyroid localization in adults, including ultrasound, parathyroid scintigraphy, CT, MRI, and angiography, although these adult series differ from most paediatric cases in that they often include previously operated patients.24-33 In addition, there are differences in the radiology of primary hyperparathyroidism as it presents in children; in particular, sporadic (non-familial) PHPT is almost always caused by a single adenoma in
children and adolescents\textsuperscript{1,2,4,6} whereas hyperplasia of all four parathyroid glands and multinodular disease are more common in adults.\textsuperscript{34}

**Ultrasound**

Ultrasound of the neck has been proposed as the optimal parathyroid localization technique, although adult series have found varying sensitivities of 34–92\% (mean 65\%) with specificities ranging from 75–96\%.\textsuperscript{24,25} Neck ultrasound is relatively inexpensive, does not involve ionizing radiation, and is performed as a real-time study. However, the success of the technique is operator-dependent and it is of no value in evaluating the retrotracheal area and superior mediastinum, because the sound wave is attenuated by tracheal air or the sternum. The tracheoesophageal area is also difficult to visualize with ultrasound. In addition, there may be difficulties in distinguishing the parathyroid glands from thyroid nodules or lymph nodes.\textsuperscript{24,25}

While ultrasound was diagnostic in two of our patients, it gave misleading information in two others in whom bilateral hypoechoic nodules, suspicious for parathyroid abnormalities, were seen. Unilateral lesions were proven at surgery in both of these patients. In a third patient with a mediastinal adenoma, ultrasound was falsely positive for a lesion in the neck. Ultrasound was falsely negative in two other patients (one early in the study period when ultrasound was technically inferior).

**Parathyroid scintigraphy**

\textsuperscript{99m}Technetium-\textsuperscript{201} thallium subtraction parathyroid scintigraphy is reported to be very specific for locating abnormal parathyroid glands but can be technically difficult to perform and is subject to well-recognized limitations.\textsuperscript{20,24,26} In a review of published series of patients with no previous parathyroid surgery, Dopman and Miller found sensitivities of 42–74\%, with a mean of 55\%.\textsuperscript{24} This technique was diagnostic in two of our patients while it was equivocal and technically suboptimal in two other patients. Recently, \textsuperscript{99m}technetium-sestamibi has been promoted as a sensitive parathyroid imaging agent in adults. This agent appears to concentrate in parathyroid tissue in accordance with the amount of mitochondrial activity, lesion size, and vascularity.\textsuperscript{27} This property provides for superior localizing ability compared to other radionuclides such as thallium or technetium alone, while delivering a smaller radiation dose. Prior to scanning, Tc-sestamibi is given intravenously alone, or in combination with oral \textsuperscript{123}I for a subtraction study. Early reports in adults report this agent as 88–100\% sensitive for parathyroid adenomas and hyperplasia.\textsuperscript{28,29} It was diagnostic in the only patient of ours in whom it was attempted.

**Computed tomography**

CT of the neck and upper mediastinum has fallen into relative disfavour in the evaluation of the hyperparathyroid patient, whether adult or child. CT allows for thin-section evaluation of the neck, including the tracheoesophageal groove and the retrotracheal area which cannot be well evaluated on ultrasound. One comprehensive series comparing CT, ultrasound, and MRI in previously unoperated patients reported CT to be 74\% sensitive and 95\% specific for the detection of parathyroid pathology.\textsuperscript{30} CT was falsely negative in both of our patients in whom it was obtained. One of these patients had an adenoma in the lower right neck, and the other had an adenoma within the superior mediastinum.

**Magnetic resonance imaging**

Several large series assessing the utility of MRI in the evaluation of the adult hyperparathyroid patient have been published in recent years. In patients without previous parathyroid surgery, MRI has been reported to be 74–78\% sensitive and 88–95\% specific, for an overall accuracy of 90\%.\textsuperscript{30,31} There are potential pitfalls in MRI imaging of the hyperparathyroid patient.\textsuperscript{30,31} Intrathyroidal parathyroid lesions cannot be detected in most cases. In addition, it may be difficult to distinguish parathyroid lesions from thyroid lesions or lymph nodes. As many as 40\% of adult hyperparathyroid patients have coexisting thyroid lesions.\textsuperscript{31} Although the frequency of thyroid disease is lower in children, this remains a potential disadvantage in selected patients. Patient 9 in our series had a lymph node mistakenly identified as a parathyroid adenoma while MRI failed to identify the mediastinal adenoma in patient 5.

**Angiography**

Superselective arterial digital subtraction angiography has been reported to be exquisitely sensitive and specific for the detection of parathyroid neoplasia in adults who have undergone prior unsuccessful localization surgery.\textsuperscript{32} In a series of 26 patients, Miller and colleagues reported this technique to have no false positives and a true positive rate of 62\%, compared to 38\% for manually subtracted conventional angiograms.\textsuperscript{32} It was used in one of our patients and gave a false positive result.

**Selecte venous sampling**

Selective venous sampling for PTH involves selective catheterization of the thyroidal and upper mediastinal
veins, assaying for PTH concentration. It is technically demanding and requires a two-site parathyroid hormone assay for diagnostic accuracy.\textsuperscript{21,33} It is useful mainly in patients in whom surgical exploration fails to find any abnormality of the parathyroid glands. In a series of previously operated adult patients, Sugg and colleagues found this technique to be 88% sensitive and 86% specific for parathyroid lesions.\textsuperscript{23} Selective venous sampling was technically successful in all four of our patients in whom it was used but diagnostic in only one patient in whom the two-site PTH assay was used.

The results of pre-operative localization amongst our patients with PHPT indicate that diagnostic accuracy has improved over the last 22 years. None of the four patients diagnosed early in the study had successful pre-operative localization while five out of seven of the later patients had their lesions accurately localized pre-operatively. Sensitivity and specificity of the individual imaging studies remain suboptimal however, creating controversy as to when and how pre-operative localization should be used.

**Should pre-operative localization techniques be used for paediatric patients with PHPT?**

The current recommendation from the National Institutes of Health is not to image adult patients with PHPT prior to their initial surgery.\textsuperscript{24} The success rate for experienced parathyroid surgeons at initial exploration is approximately 95%.\textsuperscript{24} At present, none of the localizing studies available to the radiologist can approach this figure, with the possible exception of \textsuperscript{99m}Tc-sestamibi scintigraphy, which appears promising in some adult studies.\textsuperscript{28,29} Furthermore, in adults, pre-operative localization has not been proven to shorten operating time, reduce complications, or prevent unsuccessful initial surgeries.\textsuperscript{24}

Our experience with pre-operative imaging is similar to that of adult studies, indicating that the currently available imaging studies have less than perfect sensitivity and specificity when applied to a paediatric population. In our patients, surgical outcome was excellent and unrelated to the accuracy of pre-operative localization. However, all but one of our patients had pre-operative imaging studies performed, and therefore we cannot make conclusions about surgical outcome in children in the absence of pre-operative imaging. Because PHPT is much less common in children than in adults and is usually caused by a single adenoma, we believe that in these patients it is reasonable to perform simple and inexpensive pre-operative imaging studies. Our data suggest that when imaging studies such as ultrasound and parathyroid scans are used in combination, the accuracy of pre-operative localization improves. However, pre-operative imaging, regardless of the accuracy, is not a substitute for surgical expertise, as surgical exploration is the best localization method for lesions located in the neck.

**Conclusions**

Primary hyperparathyroidism remains a rare disease in children and adolescents. Unlike in adults, there is no evidence to support screening for hypercalcaemia in asymptomatic children, because prevalence is low and there are no studies which have examined the benefits of early treatment of asymptomatic children. However, symptomatic PHPT is not a benign disease in children, and is frequently overlooked in the evaluation of children with non-specific gastrointestinal, neurological, and musculoskeletal complaints. In our experience, end-organ damage was universally present in symptomatic children by the time of diagnosis. In addition, both the duration of symptoms and the PTH level correlated with the volume of the lesion, suggesting disease progression over time. For these reasons, although PHPT is rare in children, paediatricians and other physicians caring for children should consider primary hyperparathyroidism in their differential diagnosis of unexplained non-specific complaints.

With the currently available sensitive PTH assay, it is easy to establish the diagnosis of PHPT with certainty and a minimum of investigations—measurement of serum calcium (total or ionized), phosphate, and PTH. The next step is to look for end-organ damage through skeletal surveys, renal ultrasound and slit-lamp examination. Whether pre-operative imaging is necessary in paediatric patients needs further study. In the meantime, it is reasonable to perform simple, non-invasive studies such as ultrasound and parathyroid scans.

**References**

5. Rapaport D, Ziv Y, Rubin M, Huminer D, Dintsman M.


