An analysis of surveillance screening for SDHB-related disease in childhood and adolescence

Nicola Tufton1,2, Lucy Shapiro2,3, Anju Sahdev4, Ajith V Kumar5, Lee Martin3, William M Drake1,2, Scott A Akker1,2 and Helen L Storr2,3

1Department of Endocrinology, St Bartholomew’s Hospital, Barts Health NHS Trust, London, UK
2Centre for Endocrinology, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK
3Department of Paediatric Endocrinology, Royal London Hospital, Barts Health NHS Trust, London, UK
4Department of Radiology, St Bartholomew’s Hospital, Barts Health NHS Trust, London, UK
5North East Thames Regional Genetics Service, Great Ormond Street Hospital, London, UK

Correspondence should be addressed to H L Storr: h.l.storr@qmul.ac.uk

Abstract

Objective: Phaeochromocytomas (PCC) and paragangliomas (PGL) are rare in children. A large proportion of these are now understood to be due to underlying germline mutations. Here we focus on succinate dehydrogenase subunit B (SDHB) gene mutation carriers as these tumours carry a high risk of malignant transformation. There remains no current consensus with respect to optimal surveillance for asymptomatic carriers and those in whom the presenting tumour has been resected.

Method: We undertook a retrospective analysis of longitudinal clinical data of all children and adolescents with SDHB mutations followed up in a single UK tertiary referral centre. This included index cases that pre-dated the introduction of surveillance screening and asymptomatic carriers identified through cascade genetic testing. We also conducted a literature review to inform a suggested surveillance protocol for children and adolescents harbouring SDHB mutations.

Results: Clinical outcomes of a total of 38 children are presented: 8 index cases and 30 mutation-positive asymptomatic carriers with 175 patient years of follow-up data. Three of the eight index cases developed metachronous disease and two developed metastatic disease. Of the 30 asymptomatic carriers, 3 were found to have PGLs on surveillance screening.

Conclusions: Surveillance screening was well tolerated in our paediatric cohort and asymptomatic paediatric subjects. Screening can identify tumours before they become secretory and/or symptomatic, thereby facilitating surgical resection and reducing the chance of distant spread. We propose a regular screening protocol commencing at age 5 years in this at-risk cohort of patients.

Introduction

Almost 40–50% of all phaeochromocytomas (PCC) and paragangliomas (PGL) (together known as PPGLs) are now thought to be associated with germline mutations (1, 2), but within the paediatric population this figure is higher (70–80%). Therefore, it is recommended that all children and adolescents presenting with PPGL should be offered genetic testing (3, 4). The most commonly associated genes in children presenting with PPGL (aged ≤21 years)...
are VHL (38%), followed by SDHB (25%), SDHD (7%) and RET (6%) (4). Familial PPGLs have an earlier onset (2), are more often bilateral (5) and are more likely to recur (5) when compared to sporadic tumours.

SDHB mutations are inherited in an autosomal dominant manner and have a lifetime penetrance of 30–40% (6). Individuals carrying SDHB mutations command special attention as they contribute a high proportion of the PPGLs occurring in paediatric patients (3) and have a high rate (up to 30%) of malignant transformation (7, 8). Approximately 72% of metastatic PPGLs in childhood are associated with SDHB mutations (3). This emphasises the importance of lifelong, regular surveillance for all children carrying SDHB mutations in an experienced centre as, although hard to prove, it is generally accepted that early detection and timely resection of SDHB-associated tumours will reduce the risk of metastatic disease.

Despite widespread acceptance that individuals who carry SDHB mutations should undergo regular surveillance imaging, there is no clear consensus regarding the optimal modality or frequency. The situation is even less clear in paediatric SDHB carriers due to the paucity of robust data, highlighted in a recent review (9). Since the discovery of SDHB mutations as a cause for PPGL syndromes, increasing numbers of genetically affected young family members are being identified and referred to specialist paediatric services (2). Hence, it is important to establish an appropriate surveillance protocol specifically for paediatric carriers. This must also consider the potential long-term risks of radiation exposure at younger ages (10) and the acceptability to young patients and their carers.

To address these fundamental issues, we performed a review of the published literature. In parallel we undertook detailed analysis of our paediatric SDHB cohort of both index cases and asymptomatic carriers to provide longitudinal data on clinical outcomes. Based on these combined data, we propose a regular surveillance protocol for screening children with SDHB mutations.

**Patients and methods**

We undertook a retrospective review of paediatric SDHB mutation-positive index cases and asymptomatic carriers managed in our UK tertiary referral centre. Although a subgroup of these patients have been previously described (11, 12), we considered that a separate analysis of this unique patient cohort was justified on account of the lack of published paediatric SDHB patient data and recent new information regarding the risks of radiation exposure in young patients (10).

Paediatric index cases were diagnosed with a PCC or PGL in childhood or adolescence (aged <20 years) between 1975 and 2011. Index cases presented to their local endocrine centres and were followed locally until after surgical resection. Inevitably, as the majority of the index cases were diagnosed before genetic testing became readily available and pre-date the introduction of familial PPGL surveillance programmes, they were followed up as per local guidance at the time of diagnosis and some were lost to follow up for a number of years before re-presenting. Once the genetic status was established (between 2003 and 2012), the index patients underwent regular surveillance in our centre.

Asymptomatic paediatric carriers were identified through cascade genetic screening of index cases. Children whose carrier status was confirmed following genetic screening were clinically assessed by an experienced paediatric endocrinologist and offered radiological and biochemical screening.

**Genetic testing**

All suspected paediatric SDHB carriers were offered genetic counselling and testing. This included index cases that presented with symptomatic PPGL or individuals with relatives known to carry SDHB mutations. Genetic analysis in at-risk children was routinely undertaken aged <5 years. However, 20 children were diagnosed genetically between the ages of 5 and 18 years when their individual risk was established, following the identification of an SDHB gene mutation in a family member. Five paediatric index patients presented before genetic testing was routinely available. The genetic status of these individuals was identified at a later date, usually after the development of a second tumour or metastatic disease. The median time from diagnosis of the first PPGL to the confirmation of the SDHB mutation was 15 years (range 0–34 years) in the index cases.

**Surveillance protocol**

Regular surveillance for SDH patients was introduced in our centre in 2003, and therefore some of these index cases pre-date systematic surveillance follow-up. From 2003, paediatric patients were reviewed with other affected family members in a dedicated family SDH clinic by adult and paediatric endocrinology consultants and clinical nurse specialists. Clinical review, including auxological
assessment, general examination, blood pressure and heart rate measurements were undertaken in all children annually. Metanephrines (urine or plasma) were measured annually from age 5 years.

**Biochemical testing**

24-hour urine metanephrine measurements were analysed by a high-performance liquid chromatography with electrochemical detection (HPLC-ED) assay for total fractionated metanephrines. Urine metanephrine:creatinine ratio was measured on spot urine samples. Plasma metanephrines (free fractionated) were analysed by LC-MS/MS. Age-specific reference ranges were used for spot urine metanephrine:creatinine ratio and plasma metanephrine results.

**Radiological imaging**

Abdominal ultrasound (US) or magnetic resonance imaging (MRI) of the neck, chest, abdomen and pelvis was performed annually, as previously described (11). The imaging was reviewed on two separate occasions as standard practice at our institution; the first radiological opinion was issued as a standard report when imaging was performed; the second was provided within a multidisciplinary meeting by an appropriate diagnostic imaging expert.

**Results**

Analysis included a total of 38 children (21 families): 8 index cases (4 male) and 30 SDHB mutation-positive asymptomatic carriers (12 male) identified through cascade genetic testing. The median duration of follow-up was 5.0 years (range 0.5–13.0 years) and 24.5 years (range 6–42 years) in the 30 asymptomatic carriers and 8 index cases, respectively. Two children were reviewed in the paediatric clinic (aged 8 and 15 years) and then lost to follow-up (after 4 and 1 year(s), respectively) and were re-referred aged 18 years. Data includes 175 patient years of follow-up initiated at either diagnosis (index cases) or the time of identification of SDHB mutation carrier status.

**Index cases**

The index cases were diagnosed at median age 15 years (range 10–18 years) (Table 1). All presented with solitary lesions with no evidence of metastatic disease. Four had abdominal PGLs, two had thoracic PGLs, one a PCC and one had a pelvic PGL. All underwent successful surgical resection of the primary tumour. Five of the eight cases (diagnosed 1989–2011) had no evidence of further disease identified by regular surveillance scanning, with a median duration since the original diagnosis of 13.8 years (6–27 years).

The remaining three children developed multiple tumours in adulthood (including 15 further PGLs and 1 papillary renal cell carcinoma (RCC)). Two of the three patients developed disseminated metastatic disease in adulthood. The time from diagnosis to development of further disease was 7.0, 13.0 and 16.5 years, respectively. The two patients with metastatic disease died aged 35 and 41 years (Table 1) with a survival time of 17 and 4 years from the diagnosis of metastatic disease, respectively. Detailed clinical descriptions of the three patients that developed metachronous and/or metastatic disease are provided in the supplementary data (see section on supplementary data given at the end of this article).

**Asymptomatic carriers**

Thirty children were found to have SDHB mutations on cascade genetic testing (Table 2). Genetic testing was undertaken at a median age of 6.8 years (range 1 month to 18.0 years) and the median age of their first clinical review was 8 years (range 1–15 years). Five children were <5 years at diagnosis and underwent annual clinical review only until the age of 5 years. Seventeen were aged 5–9 years at presentation and underwent annual 24-h urine metanephrine collections, US scanning of the abdomen and full clinical assessment. Five children aged 5–9 years underwent at least one MRI in place of an abdominal US scanning. Nine patients were 10–18 years old at diagnosis and had annual MRI.

To date, 27 of the 30 asymptomatic carriers have had no tumours identified during a median follow-up period of 5 years (range 1–9 years). Three of the 30 asymptomatic carriers (at ages 15, 16 and 18 years) were found to have abdominal PGLs (14 mm, 65 mm and 11 mm, respectively) identified on surveillance imaging (Table 2). Detailed clinical descriptions of these patients are provided in the supplementary data.

**Discussion**

The aim of the surveillance screening in SDHB mutation carriers is to detect and manage the
Table 1: Clinical details of the paediatric **SDHB** index cases.

<table>
<thead>
<tr>
<th>Kindred no.</th>
<th>Pt no.</th>
<th>Index case or asymptomatic carrier</th>
<th>Mutation</th>
<th>Gender</th>
<th>Age at diagnosis</th>
<th>Tumour</th>
<th>Size (mm)</th>
<th>Metanephrines</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Time from diagnosis to genetic testing (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>Index c.72+1G&gt;T exon 1</td>
<td>M</td>
<td>15</td>
<td>Phaeochromocytoma (1989)</td>
<td>a</td>
<td>Increased&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Adrenalectomy</td>
<td>No further disease – 27 years since diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>Index Deletion of exon 1</td>
<td>M</td>
<td>18</td>
<td>Thoracic PGL (1975) 3 × HNPGL</td>
<td>a</td>
<td>Increased&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Surgical resection</td>
<td>Surgical resection + 2 cycles chemotherapy + 6 cycles (over 20 years) MIBG (total 1313MBq) Metanephrines normalised 6 months later on repeat testing, stable in size so remains in situ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>13</td>
<td>Index c.136 C&gt;T exon 2</td>
<td>M</td>
<td>18</td>
<td>Abdominal PGL</td>
<td>45</td>
<td>Urine NA 653 nmol/day</td>
<td>Surgical resection</td>
<td>No further disease. 14 years since diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>18</td>
<td>Index c.137G&gt;A exon 2</td>
<td>F</td>
<td>10</td>
<td>Thoracic PGL (1982) Recurrence of Thoracic PGL Metastatic deposit in shoulder Spinal metastatic disease</td>
<td>60</td>
<td>Raised NA levels&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Surgical resection 5 cycles MIBG</td>
<td>4 cycles MIBG + 3 cycles chemotherapy + EBRT Surgical debulking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>20</td>
<td>Index c.141 G&gt;A exon 2</td>
<td>F</td>
<td>10</td>
<td>Thoracic recurrence Thoracic and spinal recurrence Progressive disease Abdo PGL (1988) Abdo PGL (1988) RCC</td>
<td>a</td>
<td>Increased&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Surgical resection</td>
<td>Died aged 41 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>24</td>
<td>Index c.31delAinsGGG exon 4</td>
<td>M</td>
<td>12</td>
<td>Abdo PGL (1991) 70</td>
<td>VMA negative&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Surgically resected</td>
<td>MIIB – non avid Died aged 31 years No further disease – 25 years since diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Indicates abnormal results.
clinical manifestations early, thereby reducing potentially serious complications and enhance cure rates (1, 2, 13, 14, 15, 16, 17). This is especially pertinent in young patients with SDHB mutations who have much higher reported rates of tumour metastasis (3, 14). However, this needs to be balanced with the reported low lifetime disease penetrance (8, 18, 19, 20). The risk of a child with an SDHB mutation developing disease during childhood is very low (20), but if tumours arise they are potentially more aggressive than adult-onset lesions (3), although the reason for this is unknown.

It is important to establish an appropriate surveillance protocol in childhood as early disease detection and intervention has the potential to cure a condition for which there are currently no satisfactory medical options once metastatic disease is established. The age at which screening should be commenced, the modality and the frequency are unclear, especially in asymptomatic paediatric patients. However, this population is small and well defined, lending itself well to a structured, regular surveillance programme. Surveillance screening is well-established in other hereditary cancer syndromes. A study of screening in Li-Fraumeni syndrome (21) showed an improved 3-year survival in the surveillance group vs the non-surveillance group (100% vs 21%).

The mean age for developing PPGLs in patients with SDHB mutations is 29 years (8). However, a number of SDHB-related tumours have been reported in the paediatric age range, the youngest aged 6 years (3, 8, 13, 17, 18, 19, 22, 23) (Table 3). The youngest reported child with SDHB-associated metastatic disease was 9 years old (3). The median interval from primary tumour to the development of metastatic disease was 7 years (range 0–25 years) (3). In our cohort, the time from initial diagnosis to development of metastatic disease was 13 and 17 years and the survival time from diagnosis of metastases was 17 and 4 years respectively, which is comparable to previously reported figures (3). As these index cases pre-date the introduction of the surveillance programme, it is possible that metastatic disease could have been prevented or at least identified at an early stage if the patient was undergoing regular surveillance. Survival rates in children and young adults with SDHB mutations who develop tumours at 5, 10 and 20 years are 95.8, 95.8 and 71%, respectively (3).

Urinary metanephrines are a non-invasive, sensitive method to detect secretory PPGL tumours. However, a proportion of PPGLs remain biochemically silent for a prolonged period due to lower production of catecholamines by the tumour (24, 25) and thus are not detected as abnormal by current assay’s, thereby mandating the use
Table 2  Clinical details on the 30 asymptomatic carriers, identified through cascade genetic testing.

<table>
<thead>
<tr>
<th>Kindred no.</th>
<th>Patient no.</th>
<th>Mutation</th>
<th>Gender</th>
<th>Age at genetic diagnosis</th>
<th>Age joined surveillance programme/first clinic screening</th>
<th>Tumour identified?</th>
<th>Age at diagnosis of tumour</th>
<th>Metanephrines</th>
<th>Treatment/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>c.72+1G&gt;T exon 1</td>
<td>F</td>
<td>0.4</td>
<td>4.0</td>
<td>No tumour</td>
<td>Normal</td>
<td>8 years of follow up</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>c.72+1G&gt;T exon 1</td>
<td>F</td>
<td>0.7</td>
<td>5.0</td>
<td>No tumour</td>
<td>Normal</td>
<td>7 years of follow up</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>c.72+1G&gt;T exon 1</td>
<td>F</td>
<td>4.0</td>
<td>4.0</td>
<td>No tumour</td>
<td>Normal</td>
<td>9 years of follow up</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>Deletion of whole exon 1</td>
<td>M</td>
<td>14</td>
<td>15.0</td>
<td>14 mm Abdo PGL</td>
<td>19.0</td>
<td>2nd screen³ plasma NMA 1310 pmol/L</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>Deletion of exon 1</td>
<td>F</td>
<td>15.0</td>
<td>15.0</td>
<td>No tumour</td>
<td>Normal³</td>
<td>5 years of follow up</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>Deletion of exon 1</td>
<td>F</td>
<td>9.0</td>
<td>9.0</td>
<td>No tumour</td>
<td>Normal³</td>
<td>3 years of follow up</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>Deletion of exon 1</td>
<td>M</td>
<td>6.0</td>
<td>6.0</td>
<td>No tumour</td>
<td>Normal³</td>
<td>6 years of follow up</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>c.72+1G&gt;T intron 1</td>
<td>M</td>
<td>0.8</td>
<td>5.0</td>
<td>No tumour</td>
<td>Normal³</td>
<td>1 year of follow up</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>11</td>
<td>c.79C&gt;T exon 2</td>
<td>M</td>
<td>12.0</td>
<td>13.6</td>
<td>No tumour</td>
<td>Normal³</td>
<td>2 years of follow up</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>c.118A&gt;G exon 2</td>
<td>M</td>
<td>6.5</td>
<td>7.0</td>
<td>No tumour</td>
<td>Normal³</td>
<td>6 years of follow up</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>14</td>
<td>c.136 C&gt;T exon 2</td>
<td>M</td>
<td>15</td>
<td>15.0</td>
<td>No tumour</td>
<td>Normal³</td>
<td>14 years of follow up</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>15</td>
<td>c.136 C&gt;T exon 2</td>
<td>F</td>
<td>1.5</td>
<td>1.5</td>
<td>No tumour</td>
<td>Normal³</td>
<td>5 years of follow up</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>16</td>
<td>c.136 C&gt;T exon 2</td>
<td>F</td>
<td>0.9</td>
<td>2.0</td>
<td>No tumour</td>
<td>Normal³</td>
<td>4 years of follow up</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>17</td>
<td>c.136 C&gt;T exon 2</td>
<td>F</td>
<td>4.8</td>
<td>5.0</td>
<td>No tumour</td>
<td>1st surveillance screen completed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>19</td>
<td>c.137G&gt;A exon 2</td>
<td>F</td>
<td>18</td>
<td>12.0</td>
<td>11 mm Abdo PGL</td>
<td>18.0</td>
<td>Normal³</td>
<td>9 years of follow up³</td>
</tr>
<tr>
<td>9</td>
<td>20</td>
<td>c.287-1G&gt;C exon4</td>
<td>F</td>
<td>9.0</td>
<td>9.0</td>
<td>No tumour</td>
<td>Normal³</td>
<td>Surveilance monitoring. No increase in size of PGL over 2 years. New 6 mm lesion on recent surveilance review with radiological characteristics of PGL</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>21</td>
<td>c.287-1G&gt;C exon4</td>
<td>M</td>
<td>12.0</td>
<td>12.0</td>
<td>No tumour</td>
<td>Normal³</td>
<td>5 years of follow up³</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>23</td>
<td>c.268C&gt;T exon 3</td>
<td>F</td>
<td>6.0</td>
<td>5.0</td>
<td>No tumour</td>
<td>Normal³</td>
<td>1 year of follow up³</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>26</td>
<td>c.311delAinsGG exon 4</td>
<td>F</td>
<td>6.0</td>
<td>6.0</td>
<td>No tumour</td>
<td>Normal³</td>
<td>5 years of follow up³</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>27</td>
<td>c.338G&gt;A exon 4</td>
<td>M</td>
<td>15</td>
<td>15.0</td>
<td>65 mm Abdo PGL adherent to and invasive of great vessels 12 mm Abdo PGL, bone mets</td>
<td>15.0</td>
<td>Urine NMA 2863 nmol/day, 3MT 3287 nmol/day</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>28</td>
<td>c.338G&gt;A exon 4</td>
<td>M</td>
<td>7.0</td>
<td>7.0</td>
<td>No tumour</td>
<td>Normal³</td>
<td>6 years of follow up³</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>29</td>
<td>c.406delA exon 4</td>
<td>F</td>
<td>5.0</td>
<td>5.0</td>
<td>No tumour</td>
<td>Normal³</td>
<td>3 year of follow up³</td>
<td></td>
</tr>
</tbody>
</table>
The table outlines the clinical details of the asymptomatic SDHB carriers, showing their specific mutation, age at which they underwent genetic testing, age at which they joined the surveillance programme, and outcomes of the surveillance, with tumour details if relevant. The kindred number relates to the index case in Table 1 for each family group. All asymptomatic underwent annual clinical and biochemical review, unless specified (9). Further clinical details are provided in the supplementary data for the three cases that had tumours identified on screening.

CT and functional imaging are undoubtedly useful in the management of PPGL-associated disorders, especially in the identification of metastatic disease, but involve the use of ionising radiation, the risks of which are hard to gauge in a cancer-prone syndrome. This is particularly relevant in children as the total lifetime risk of cancer induction is highest when radiation exposure occurs at younger ages. Clinicians and radiologists need to balance this increased risk when justifying high radiation dose investigations in children. The cumulative cancer risk for a young female aged <20 years following a single chest, abdomen and pelvis (CAP) CT scan is >1 in 1000 additional cancers. The lifetime risk of cancer incidence in children <9 years is estimated as 14% per Sv radiation exposure (10). These data are derived from a population without a known tumour predisposition and, although hard to prove, it is assumed that these risks will be higher in SDHB patients who have a higher background risk of tumour development. In keeping with this, Schiffman et al. supports the use of total body MRI for early cancer surveillance in young patients (14). The Endocrine Society guidelines state that MRI is indicated when radiation exposure should be limited (30), which is particularly relevant in children and individuals with known germine mutations predisposing to PPGL. Additionally, one should distinguish between the surveillance of asymptomatic
carriers and the follow-up surveillance of patients with known or previous PPGL with regard to balancing the risks and benefits of the modality of imaging used. This is particularly important in individuals who have a risk of tumour recurrence at the primary site and a higher risk of metastatic disease (3).

The acceptability of the surveillance protocol is a further consideration. Although lengthy, MRI scanning is attractive as it is associated with no radiation exposure. Young children may not tolerate long durations of time in a scanner and general anaesthesia is probably not justified for routine screening purposes. Some centres advocate the use of rapid sequence MRI (31) and this could be a viable alternative for paediatric patients. As lifelong surveillance is currently recommended, it is important to balance the need for medical intervention against the potential to provoke unnecessary distress or anxiety as this may adversely affect future engagement with surveillance screening.

Based on our data and the available published literature, we suggest a comprehensive surveillance protocol for paediatric asymptomatic SDHB mutation carriers (Fig. 1). Once a tumour is identified, further imaging for characterisation and management planning and subsequent surveillance follow up needs to be individualised. To be fully effective, a surveillance-screening programme should commence before the earliest known age of disease onset. Hence, we recommend that screening commences at age 5 years, as the earliest reported PPGL disease is at age 6 years (23). The authors recognise that this is an arbitrary age cut-off and needs to be regularly reviewed as more data become available. Consistent with the Endocrine Society guidelines, our screening protocol includes regular clinical assessment, education regarding symptoms of catecholamine excess, measurement of metanephrines and imaging (30). At all ages, it is recognised that the abdomen is the most common site of disease in SDHB carriers (3, 8, 13, 32). Our paediatric data is consistent with this, as all of the asymptomatic carriers who developed tumours and half of the index cases were found to have abdominal PGLs. This is corroborated by analysing the paediatric subgroups in previous studies demonstrating the vast majority of SDHB-related tumours in the paediatric age range were abdominal (3, 8, 13, 18, 33). Hence, annual abdominal imaging is commenced from the age of 5 years. Ideally MRI would be performed for surveillance in all individuals;

<table>
<thead>
<tr>
<th>Site of PPGL</th>
<th>Age at diagnosis (years)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal neuroblastoma</td>
<td>5</td>
<td>(22)</td>
</tr>
<tr>
<td>Abdominal PGL</td>
<td>6</td>
<td>(23)</td>
</tr>
<tr>
<td>Adrenal phaeochromocytoma</td>
<td>9</td>
<td>(18)</td>
</tr>
<tr>
<td>HNPG</td>
<td>9</td>
<td>(19)</td>
</tr>
<tr>
<td>Thoracic PGL</td>
<td>10</td>
<td>(11)</td>
</tr>
<tr>
<td>Pelvic PGL</td>
<td>16</td>
<td>(32)</td>
</tr>
<tr>
<td>RCC</td>
<td>15</td>
<td>(35)</td>
</tr>
<tr>
<td>GIST (stomach)</td>
<td>16</td>
<td>(36)</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>9</td>
<td>(3)</td>
</tr>
</tbody>
</table>

The table shows the youngest individuals diagnosed with SDHB-related tumours reported in the literature, grouped by tumour type/location.

GIST, gastrointestinal stromal tumour; HNPG, head and neck paraganglioma; PGL, paraganglioma; PPGL, phaeochromocytoma and paraganglioma; RCC, renal cell carcinoma.

Figure 1
Our suggested protocol for surveillance screening of asymptomatic paediatric SDHB gene carriers. The figure outlines our suggested surveillance protocol for asymptomatic SDHB gene carriers in the paediatric population based on our data and the available published literature. It shows the different routes by which children are referred for genetic testing, and what should be included in their annual clinical review depending on the age of the child. *However, it should be noted that this protocol should be adapted depending on the maturity of the individual child and the families’ wishes.
however, as MRI may not be tolerated in younger children, we suggest abdominal US scanning as a possible alternative in asymptomatic patients aged 5–10 years (with normal biochemistry). However, it is important to recognise the limitations of US scanning, particularly its lower sensitivity and specificity for tumour detection (although generally higher in children than adults due to slimmer body habitus), so MRI should be introduced as early as is tolerated, without the need to subject the child to the risk of GA or inducing unnecessary anxiety. As MRI has a much higher sensitivity for detecting tumours compared to US, we recommend from the age of 10 years, or earlier if tolerated, annual non-contrast MRI of neck, thorax, abdomen, thorax and pelvis alternating with abdominal MRI are performed, in line with our adult protocol (11). The rationale for this is that the earliest reported SDH-related disease at body sites other than the abdomen is aged 9 years (19, 34, 35, 36). If metanephrines are raised and abdominal imaging does not identify the tumour, other body sites should be investigated. Given the high reported malignancy rate of paediatric PPGLs (3) and the limited data available in childhood, we are currently performing annual imaging in addition to detailed clinical review. However, we expect that this will be extended to 18–24 monthly in line with adult protocol(s), as more data is reported.

Despite the relatively low penetrance of SDHB disease in children and adolescents, the associated tumours cause significant morbidity and mortality, and therefore the authors believe that regular surveillance is warranted. The authors believe that all children that are identified as SDHB carriers should be entered into prospective surveillance programmes. The aim of any SDHB surveillance programme must be to identify disease early, improve cure rates and limit the chance of malignant transformation. Surveillance programmes have inherent drawbacks including the cost burden/resource constraints to the health system and also anxiety/inconvenience to the patients. Any screening programme risks turning otherwise well and healthy individuals into patients. The surveillance programme for SDHB mutation carriers should begin before the risk of tumour formation. Tumours would then be identified and resected in a timely fashion, perhaps even before they become secretory.

Supplementary data
This is linked to the online version of the paper at https://doi.org/10.1530/EC-18-0522.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding
N T is funded by a grant from The Medical College of St Bartholomew’s Hospital Trust (registered charity number 1115519).

Ethics statement
This study was carried out in accordance with the Declaration of Helsinki and all the applicable local regulations. As this is an analysis on subjects’ data taken during normal clinical practice, no specific authorisation by ethic committee was sought.

Author contribution statement
N T and L S collated the data. L M, S A A, W M D and H L S have clinical care of the patients. All authors contributed to the writing of the manuscript.

References


Received in final form 22 January 2019
Accepted 28 January 2019
Accepted Preprint published online 29 January 2019