**Multiple Endocrine Neoplasia in Children and the Importance of Screening: Part 2**

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This article continues as part of a two part series in exploring the importance of screening in multiple endocrine neoplasia, with emphasis on Von Hippel Lindau Disease, why screening is important and the role of the paediatric endocrine nurse.

**Von Hippel Lindau disease (VHL)**

VHL is another type of multiple endocrine neoplasia, and is inherited in an autosomal dominant manner like MEN1. Some families may have the VHL diagnosis without genetic testing, due to two or more clinical manifestations having been noted. The gene mutation is located at 3q26-25, so the long arm of chromosome 3, locus 26-25. The most common tumours identified within this syndrome are retinal and central nervous haemangioblastomas, renal cancers, renal, pancreatic and epididymal cysts, phaeochromocytomas and paragangliomas (Maher et al. 2011).

VHL disease can be classified into subtypes, relating to whether there are phaeochromocytomas present. Clinical presentation can manifest usually in adulthood (Prasad et al. 2011), but can also present much earlier in childhood, resulting in the need for a screening protocol as seen in Table 3.

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**Table 1: Screening protocol for children with VHL disease (Johnston et al. 2000)**

Phaeochromocytomas are less common in children, usually occuring in approximately 10% of cases (Johnston et al. 2000), and manifest in around 1% of all hypertensive adolescents (Gonc et al. 2011). They can be life threatening if not detected early enough and treated accordingly (Horton et al. 1976). Phaeochromocytomas are tumours of the adrenal medulla excreting excessive catecholamines, ie noradrenaline (norepinephrine), adrenaline (epinephrine) and dopamine, and regular screening for these tumours include annual blood pressure measurements, x3 24hour urine collections alongside plasma samples (van Berkel et al. 2014). Surgery is the treatment of choice (Waguespack et al. 2010), with medical therapeutic intervention needed beforehand. Oral alpha-blockades are the therapy of choice, usually Phenoxybenzamine, an alpha receptor antagonist, which can improve symptoms by lowering blood pressure (Waguespack et al. 2010, Ramachandran R 2017), or Doxazosin (Havekes et al. 2009), a selective alpha-1-receptor antagonist (Lenders et al. 2014). Clearly, careful observations of blood pressure are needed during and post surgery. Of note, if this is the second adrenal gland to have been operated on, the child will be rendered cortisol deficient, and management for cortisol replacement with hydrocortisone should be put into place. Careful monitoring of potential signs and symptoms of phaeochromocytomas in children with the known VHL gene mutation is necessary, and can start from as young as five years of age (Priesemann et al. 2006).

Annual review by ophthalmology with fundoscopy and fluorescein angiography can identify any retinal lesions, which can occur more commonly than phaeochromocytomas, in 60% of all cases. Cerebellar haemangiomas can occur in approximately 60% of VHL cases (Johnston et al. 2000), and also spinal cord or medulla oblongata tumours, which can occur less frequently in around 8-14% of all VHL cases (Horton et al. 1976), resulting in the need for regular imaging, but from the age of 10 years.

**The importance of screening**

It is vital that any child presenting with one of these neuroendocrine tumours, or other clinical manifestations, is genetically tested, with or without a family history (Lenders et al. 2014), and genetic counselling and discussion of ethical implications should be borne in mind. Screening children in at-risk families has been shown to reduce mortality and morbidity (Prasad et al. 2011), and can clearly identify lesions prior to the child becoming symptomatic. This can reduce the risk of further complications which can sometimes be fatal, especially with regards to phaeochromocytomas (Johnston et al. 2000). Screening programmes for disease are widespread internationally, and can offer patients clear guidance on how to make informed choices with regards to the specific disease process, but also support, when and where needed. Screening can improve quality of life by identifying disease early, or even save lives. Programmes are not mandatory, but it is clear how beneficial they are, potentially allay fears, or reduce the risk of further clinical manifestations. The protocols detailed here are suggestions from one paediatric endocrine centre with a large cohort of MEN patients, principally due to the links with the fellow adult endocrine department (Johnston et al. 2000). They are used as a clinical tool in order to allow early treatment and early intervention, and this continued surveillance is advised (Priesemann et al. 2006). Box 2 describes a case study demonstrating continued surveillance in a child and his family.

**Box 2: Case study**

Tom is a boy with a family history of VHL, tested positive for the VHL gene as a baby, and commenced the screening programme at age 5 years. His father was positive, as was his older teenage brother and teenage female cousin: they were known well to the paediatric endocrine clinic, and regularly attended their screening appointments.

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**Figure 1**

**Tom’s family tree**

When Tom was 9 years old, his urinary catecholamines levels were raised, but he was asymptomatic. A year later when he was 10 years old, a lesion was noted on an abdominal MRI scan, which was a paraganglioma in the upper retroperitoneum, interposed between the aorta, inferior vena cava, and portal vein. This was excised when he was 11 years old. Another paraganglioma was subsequently found and, as Tom continued to have raised urinary catecholamines, and was now symptomatic, he was commenced on Doxazocin. When Tom turned 13 years old, a small phaeochromocytoma was noted on MRI on his left adrenal gland. At this stage, Tom was noted to be very upset in his clinic appointments, and psychological intervention and support was commenced for Tom and his family. The following year showed an islet cell tumour on his routine MRI, and then another larger phaeochromocytoma on his right adrenal gland, for which he underwent a right adrenalectomy.

Following this, Tom was clinically asymptomatic, although his urinary catecholamines were still raised. However, the following year he became symptomatic again, and then underwent a left adrenalectomy. Now that Tom had had both of his adrenal glands removed, he had to be commenced on hydrocortisone and fludrocortisone replacement, and a full educational training package was implemented by the paediatric endocrine nurse specialist. Following this, Tom is now transitioning to the adult endocrine clinic, which his father and the rest of extended family attends.

**Patient support and the Nurses role**

Patient support groups for children and families with MEN are active within the UK and around the world, which offer and support advice online and at group meetings. Advice on lifestyle, coping mechanisms and also resources are available, some of which are child friendly. Nurses and other healthcare professionals are all active within these groups, helping to provide patient information literature.

The paediatric endocrine nurse specialist’s (PENS) role is varied (Hamric and Spross 1989, Miller 1995, Gibson 2001, McCreaddie 2001, Austin et al. 2006, Llahana 2005) as seen in Figure 2

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**Figure 2: The multifaceted role of the paediatric endocrine nurse specialist (PENS)**

It is clear to see how these many roles are necessary in caring for a child and their family with a MEN syndrome. It is often the PENS that manages and liaises the timings of the continued surveillance programmes, by using some type of database support system with alerts on when the next part of the screening programme is due, so the Liaison and Patient Advocate roles are really dominant. In addition, the Educator role is also at the forefront, in advising on the disease process, and also if further input is required, such as the need for cortisol replacement in the instance of bilateral adrenalectomy. However, full multi-disciplinary team management of these families, including geneticists, adult and paediatric endocrine teams, endocrine surgeons, and teams from other specialities, is required in order to provide the best care. Liaison with adult endocrine nurse colleagues is strongly recommended during Transition.

**Conclusion**

Screening and surveillance programmes are vital for children and their families with inherited endocrine neoplasia syndromes. Children can be identified if they are at risk early, if they are from families with identified genetic disorders: subsequently, the screening can commence at the appropriate time in order to identify any clinical manifestations as early as possible. The paediatric endocrine nurse specialist is key within the multidisciplinary team in acting as the patient advocate, and liaising with the various team members.

**Resources**

UK MEN support group: [www.amend.org.uk](http://www.amend.org.uk)

USA MEN support group: [www.amensupport.org](http://www.amensupport.org)

Australia NET support group: [www.unicornfoundation.org.au](http://www.unicornfoundation.org.au)

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