**Multiple Endocrine Neoplasia in Children and the Importance of Screening: Part 1**

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**Introduction**

Endocrine tumours are tumours, or neoplasms, that arise from endocrine glands, or tumours that secrete hormones irrespective of the site of origin (Sarvida and O'Dorisio 2011). Most commonly in children, tumours can originate in the pituitary, thyroid and adrenal glands, and germ cell tumours, but can also include neuroendocrine tumours , which are types of tumours that have originally arisen from the neural crest. This article will explore the diagnosis and management of neuroendocrine tumours in children, predominantly by discussing inherited endocrine neoplasia syndromes, the importance of developing and implementing screening programmes and how they impact clinical care, and finally the importance of patient support groups and the role the paediatric endocrine specialist nurse plays in supporting patients and their families.

**Neuroendocrine tumours in children**

Most neuroendocrine tumours (NETs) occur sporadically and are non-hereditary (Howell and O'Dorisio 2012); however, some can be due to varying types of inherited endocrine neoplasia syndromes, or Multiple Endocrine Neoplasia (MEN) (Johnston et al. 2000). These children can present with clinical signs or symptoms due to the excess hormone being released. In specially run NET / MEN clinics for children, new non-symptomatic referrals are received from fellow ‘Adult’ Endocrine clinics with adult NET patients who have had children; these adults are keen for genetic testing for their children, and, if proven positive, can commence a regular screening programme. The ethics of consent and future counselling in genetic testing in children raises many issues, but, experientially, parents with the identified gene have either wanted the genetic test done on their child to confirm the need for annual screening, or wanted them to enter a non-invasive screening programme, until potential symptoms may develop. Conversely, if proven that the child has not inherited the mutation, then they can be excluded from further follow up.

Adults with NETs is a rare phenomenon, with the incidence estimated at 5.25 per 100,000 (Diets et al. 2017). The incidence amongst children is even more rare, at approximately 2.8 NETs per million children (Howell and O'Dorisio 2012). The management and treatment of a NET will depend on the site of the tumour, and how it is affecting the child. It will also depend on if the child has one of the MEN syndromes, as obviously treatment and management are different for the different types. Usually, the tumour will need some type of resection, whether partial or total, where a total resection remains the treatment of choice if possible, for the chance of complete cure.

**MEN Type 1**

MEN1 is an autosomal dominant disorder, meaning an affected parent has a 50% chance of having an affected child. The abnormal MEN1 gene is located at 11q13 (Falchetti 2017) (locus 13 on the long arm of chromosome 11), and is characterized by the occurrence of tumours of the ‘Three P’s’: Pituitary adenomas, Parathyroid gland tumours, and Pancreatic tumours (Newey et al. 2009). There is currently no evidence of any genotype-phenotype relationship, so affected people are characterized by their genetic status. Hyperparathyroidism is very common, occurring in approximately 90% of cases (Johnston et al. 2000), resulting in the need for annual measurements of serum calcitonin and parathyroid hormone (PTH) levels. Some may advocate parathyroidectomy, but there is the potential for regrowth of any residual tissue: the other school of thought is to wait until the child is symptomatic.

Pancreatic islet cell tumours can be multifocal, and have a reduced frequency of occurrences, yet still high at around 80% (Johnston et al. 2000), and can often be found in adolescence. Annual serum measurements of pancreatic polypeptides and gastrin levels should be performed for children at risk, alongside regular pancreatic imaging. Surgery is difficult due to the risk of developing Type 1 Diabetes.

Pituitary adenomas are less common, with an occurrence of approximately 10 – 65% in children (Johnston et al. 2000), and usually secrete prolactin or growth hormone, thereby resulting in the need for annual measurements of serum prolactin and IGF-1 levels, and pituitary MRI imaging. Transsphenoidal surgery for further resection is needed if there is no medical response for a prolactinoma, showing that treatment is the same for any other non MEN pituitary tumour (Brandi et al. 2001). Screening can start earlier in childhood around the age of 10 years of age (Newey et al. 2009). Table 1 advises the screening protocol for children with MEN1.

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**Table 1: Screening protocol for children with MEN1 (Johnston et al. 2000)**

**MEN Type 2a**

The gene mutation for MEN2 is the RET proto-oncogene (10q11), so is on the long arm of chromosome 10 at locus 11 (Raue and Frank-Raue 2010). Medullary thyroid carcinoma (MTC) is the most common clinical manifestation, combined with hyperparathyroidism and phaeochromocytomas, which are catecholamine secreting tumours from the adrenal medulla. MEN2a is the most common type of the MEN syndromes, and it is recommended that children with the RET mutation MEN2a are screened from age 5 years, looking at urinary catecholamine measurements and blood pressure monitoring, serum calcium levels, and regular imaging of the adrenal glands. If the gene mutation is known, then a radical prophylactic thyroidectomy is advised from this age, due to reports of C cell hyperplasia in the thyroid gland, from at least the age of 3 years (Johnston et al. 2000), showing that early intervention is vital in the hope of a cure (Punales et al. 2008). Diagnosis of C cell hyperplasia is confirmed by serum calcitonin levels, and thyroid tissue biopsy by FNA (fine needle aspiration) with simultaneous ultrasound imaging. If the gene mutation is not known, then annual pentagastrin stimulation tests are advised (Butler and Kirk 2011) (See Box 1). A recommended screening protocol for children is seen in Table 2.

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**Table 2: Screening protocol for children with MEN2A (Johnston et al. 2000)**

**Box 1: The pentagastrin stimulation test**

Basal samples of calcitonin should be taken as per the hospital policy. 0.5mcg/kg should be administered IV as a small bolus, over 10-15 seconds: as very small amounts are needed, so the pentagastrin can be diluted in a few mL of saline for administration. Samples are taken as per below: (Butler and Kirk 2011)

 (insert table below here)

Children and their families need to be advised of potential side effects, such as flushing, nausea, dizziness, or bradycardia, and prepared for intra-venous cannulation as per the hospital protocol. Due to the side effects it is advised that the child lies down for the duration of the test. Nurses carrying out the test should have the equipment ready and the Biochemical Laboratory warned in advance, as the samples have to be delivered immediately on ice. Calcitonin is known to be sensitive to pentagastrin (Machens et al. 2008), a synthetic polypeptide. MTC is a malignancy of the calcitonin secreting cells in the thyroid gland: therefore, increased levels are related to malignancy, and can indicate that surgical resection is necessary (Barbot et al. 1994). Even after thyroidectomy, it is advised that pentagastrin stimulation tests are still carried out in order to detect any residual C cells.

|  |  |
| --- | --- |
| Time (min) | Calcitonin |
| 0 | + |
| 1 | + |
| 2 | + |
| 3 | + |
| 5 | + |
| 10 | + |

 **(table to be inserted into box above)**

**MEN Type 2b – Also known as MEN Type 3**

MEN2b has been characterised as being the most aggressive of the MEN syndromes (Brandi et al. 2001). The characteristics of MEN2a manifest, but, in addition, there are added complexities of mucosal and gastrointestinal ganglioneuromatosis, and also marfanoid habitus. Marfanoid habitus is a mix of clinical signs resembling Marfan syndrome, including long limbs and a high arched palate. The mucosal, non-malignant neuromas tend to occur in 100% of patients with this condition(Kirk et al. 1991), giving the lips a very characteristic swollen and sometimes bumpy appearance. They are often present at birth or within the first few years of life. MTC has also been detected shortly after birth (Johnston et al. 2000), so early prophylactic thyroidectomy is recommended as soon as possible, with the child then commencing thyroxine replacement medication. It should be stressed that screening for phaeochromocytomas should be done before any thyroid surgery, to pre-empt an intra-operative crisis (Johnston et al. 2000). In MEN2b, phaeochromocytomas can occur in up to 50% of children. Screening runs along similar lines to that of MEN2a, apart from commencing from age 3 years of age, and the earlier thyroidectomy.

**Conclusion**

This article has concluded as part one of a two part series. It has explored screening programmes involved in multiple endocrine neoplasia in children, focusing on MEN 1, 2a and 2b. The concluding part will focus on another type of multiple endocrine neoplasia, Von Hippel Disease, by exploring the pathophysiology, detailing a case study, emphasising the importance of screening programmes, and by looking at the role of the paediatric endocrine nurse specialist.

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