PTEN Hamartoma Tumour Syndrome - Unravelling the Complexities of Childhood Surveillance

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Background

•PTEN hamartoma tumour syndrome (PHTS), which encompasses Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome and Proteus syndrome, is a rare autosomal dominant inherited disorder characterised by macrocephaly, multiple hamartomas and an increased risk of several cancers (breast, endometrial and thyroid).

•PTEN (phosphate and tensin homologue deleted on chromosome ten) encodes a ubiquitously-expressed tumour suppressor phosphatase that regulates cell survival and migration.

•Clinical diagnostic criteria for PTEN testing, Fig. 1, are established, however increasing evidence highlights a broader spectrum of clinical features associated with PTEN mutations, adding to the challenges surrounding diagnosis, surveillance and counselling.

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Figure 1. The Cleveland Clinic criteria for adult and paediatric subjects has been demonstrated to be superior in performance to the current National Comprehensive Cancer Network (NCCN) clinical criteria (1) in selection of patients for PTEN mutation screening (2). Paediatric criteria (blue) includes macrocephaly and at least one of four additional criteria.

Centre Experience

•We manage two siblings from a consanguineous Bengali family, with a confirmed germline truncating mutation in PTEN (R233X), Fig. 2, inherited from their mother.

•Mother developed cutaneous lipomas, Hashimoto’s thyroiditis and a compressing thyroid goitre requiring near-total thyroidectomy at the age of 28 years.

•Both children have macrocephaly and developmental delay with autistic-spectrum features but are otherwise asymptomatic (age 7 years and 6 years).

Aims and Methods

•Published guidelines (1) are available for adult patients with positive genetic testing but screening in children is currently not standardised. Moreover, there is poor genotype-phenotype correlation and age-related penetrance in PTEN mutations, making decisions surrounding appropriate paediatric surveillance complex.

•Clear evidence-based surveillance strategies for these individuals are required. We aimed to perform a systematic search and review of the medical literature for existing guidelines and epidemiological data to produce a comprehensive screening plan for our paediatric PHTS patients.

•We carried out a primary search of Medline through PubMed and secondary searches through the NHS Evidence National Library of Guidelines and the Cochrane Database.

Results

•We identified 2 published guidelines, NICE guidelines and NCCN guidelines (1). Limited screening was advocated in patients <18yrs unless there was a family history of cancer <23yrs of age. No specific recommendations were found on the management of paediatric patients with a positive genetic diagnosis of PHTS.

•12 relevant papers were also identified, including the first prospective study reported to clarify corresponding cancer risks (3).

•For thyroid cancer the reported early onset of elevated risk from birth, Fig. 3, which is sustained throughout life is of key clinical interest (3). Case reports and series highlight the paediatric presentation of PHTS-associated thyroid neoplasia and the importance of screening ultrasounds, as early detection has been clearly shown to improve outcome (4).

Conclusions and Recommendations

•There is little available guidance for the surveillance in childhood of patients with PTEN mutations, who are at increased risk of developing thyroid cancer.

•We recommend an early approach to surveillance of paediatric PHTS patients, including regular thyroid ultrasound scans, and comprehensive surveillance for clinically significant but non-malignant features such as arteriovenous malformation and autism.

Figure 2. Panel A: Chromatogram of R233X mutation; Top figure wild type (C/C), bottom figure heterozygous patient mutation (C/T). Panel B: Pedigree: light shading – macrocephaly, dark shading – macrocephaly and confirmed mutation positive

Figure 3. Age related penetrance curve for thyroid cancer demonstrating the early childhood onset of elevated risk, which is sustained throughout life (4).