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PTEN Hamartoma tumor syndrome in childhood: A review of the clinical literature

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Abstract

PTEN hamartoma tumor syndrome (PHTS) is a highly variable autosomal dominant condition associated with intellectual disability, overgrowth, and tumor predisposition phenotypes, which often overlap. PHTS incorporates a number of historical clinical presentations including Bannayan-Riley-Ruvalcaba syndrome, Cowden syndrome, and a macrocephaly-autism/developmental delay syndrome. Many reviews in the literature focus on PHTS as an adult hamartoma and malignancy predisposition condition. Here, we review the current literature with a focus on pediatric presentations. The review starts with a summary of the main conditions encompassed within PHTS. We then discuss PHTS diagnostic criteria, and clinical features. We briefly address rarer *PTEN* associations, and the possible role of mTOR inhibitors in treatment. We acknowledge the limited understanding of the natural history of childhood-onset PHTS as a cancer predisposition syndrome and present a summary of important management considerations.

KEYWORDS

autism spectrum disorder, Bannayan-Riley-Ruvalcaba syndrome, cowden syndrome, PHTS, PTEN hamartoma tumor syndrome

1 | INTRODUCTION

PTEN (Phosphatase and tensin homolog deleted on chromosome 10) is a tumor suppressor gene on chromosome 10q23 (Li et al., 1997). Germline pathogenic variants in the *PTEN* gene can give rise to hamartomatous overgrowth syndromes collectively known as *PTEN* hamartoma tumor syndrome (PHTS). These include Cowden syndrome (CS), Bannyan-Riley-Ruvalcaba syndrome (BRRS) (Marsh et al., 1997, 1999) Lhermitte-Duclos Disease (LDD) in adults (Zhou et al., 2003) and autism-macrocephaly (Butler et al., 2005; Conti et al., 2012). A body of evidence indicates that they represent variable expression and age-related penetrance of one condition, as opposed to allelic conditions (Arch et al., 1997; Lachlan, Lucassen, Bunyan, & Temple, 2007; Marsh et al., 1999; Merks, 2003; Zori, Marsh, Graham, Marliss, & Eng, 1998).

Familiarity with the origins of these syndromes is useful in understanding the different phenotypes associated with PHTS, their overlap and how this relates to current clinical diagnosis and genetic testing. The gene is highly conserved and all types of pathogenic variants have been reported (whole exonic deletions, loss of function, missense and promoter) with no clear genotype–phenotype correlation (Smith, Thacker, Seyfi, Cheng, & Eng, 2019).

While this review is focussed on pediatric patients, some discussion of adult presentation and medical issues is included because 60–90% of *PTEN* pathogenic variants are inherited (Mester & Eng, 2012), it is vital to have knowledge of the presentations and medical issues affecting adults with the condition, so that appropriately tailored family history can be elicited to facilitate diagnosis and to enable discussion about prognosis.

Of note, much of the PHTS literature is made up of case reports and small case series (this is especially the case for the pediatric literature). When such small patient numbers are involved, clinicians must be alert to the inherent risks of selection bias. In the case of very rare associations, there is a possibility that such associations may not be

real, and this is especially true for historic (pre-molecular diagnosis) publications.

2 | *PTEN* HAMARTOMA TUMOR SYNDROME

BRRS is characterized by congenital macrocephaly (>2 standard deviations [*SD*]), freckling of the glans penis, hamartomatous intestinal polyps, arteriovenous malformations (AVM), autism, developmental delay or intellectual disability, and lipomas.

The condition was first described by Riley and Smith in 1960 as a "Macrocephaly, Pseudopapilloedema and Multiple Hemangiomata" syndrome in a mother and four affected children (Riley & Smith, 1960). Separately, in the 1970s Bannayan and later Zonana described syndromes of macrocephaly, angiomatosis and lipomatosis, and of bowel hamartomas and finger overgrowth (Bannayan, 1971; Zonana, Rimoin, & Davis, 1976). Several publications of similar syndromes followed with pigmentation of the glans penis being added to the phenotype (Dvir, Beer, & Aladjem, 1988; Fargnoli, Orlow, Semel-Concepcion, & Bolognia, 1996; Ruvalcaba, Myhre, & Smith, 1980). In 1988 Gorlin, through observations in his own patient, noted the overlap between these conditions and coined the term BRRS and he later published a series of individuals with these condition with the additional finding of Hashimoto's thyroiditis (Gorlin, Cohen, Condon, & Burke, 1992).

CS is also characterized by macrocephaly, with mucocutaneous abnormalities (facial trichilemmomas, keratosis of the hands and feet, papillomatous papules), and benign and malignant tumors of the breast, thyroid, endometrium, and kidney.

In 1963 Lloyd and Dennis described the eponymous patient of the syndrome, Rachel Cowden, with a constellation of craniofacial features (mandibular and maxillary hypoplasia, high arched palate, underdeveloped soft palate and uvula, and microstomia) mucocutaneous features, (papillomatosis of the lips and oropharynx, scrotal tongue) skeletal abnormalities (pectus excavatum, scoliosis) and benign growths (multiple thyroid adenomas, fibrocystic disease of the breast) who died of ductal breast carcinoma (Lloyd & Dennis, 1963). Multiple publications further delineated the phenotype, with focus on the characteristic dermatological features, leading to the development of clinical diagnostic criteria (Brownstein, Mehregan, Bikowski, Lupulescu, & Patterson, 1979; Starink et al., 1986; Weary, Gorlin, Gentry, Comer, & Greer, 1972).

LDD is a dysplastic gangliocytoma of the cerebellum and may present with ataxia or symptoms of raised intracranial pressure (Lhermitte & Duclos, 1920; Wang, Zhang, Cheng, Liu, & Hui, 2017). It was associated with CS before identification of the *PTEN* gene (Padberg, Schot, Vielvoye, Bots, & de Beer, 1991).

PTEN was identified as a major causative gene for the CS phenotype in 1997 (Liaw et al., 1997; Nelen et al., 1996). The same gene was implicated in BRRS (Arch et al., 1997;Marsh et al., 1997) with further publications describing identical *PTEN* mutations in patients with CS and BRRS presentations. CS and BRRS presentations have occurred within the same family with age-related penetrance (Lachlan et al., 2007; Marsh et al., 1998; Zori et al., 1998).

PTEN pathogenic variants are also associated with macrocephaly and developmental delay/autism with variable presence of other PHTS features (Butler et al., 2005; Goffin, Hoefsloot, Bosgoed, Swillen, & Fryns, 2001; Herman et al., 2007;Marsh et al., 1999; McBride et al., 2010; Orrico et al., 2009; Varga, Pastore, Prior, Herman, & Mcbride, 2009).

3 | GENOTYPE–PHENOTYPE CORRELATION

The genotype–phenotype correlations reported are not substantial enough to facilitate prediction of phenotype or personalisation of screening tests, although there is some evidence that thyroid cancer is less common in those with a missense versus other types of pathogenic variant (Bubien et al., 2013; Mighell, Evans-Dutson, & O'Roak, 2018; Nieuwenhuis et al., 2014; I. N. Smith et al., 2019).

Functional studies have attempted to determine genotype–phenotype associations for the autism-macrocephaly PHTS phenotype and the broader cancer predisposition PHTS phenotype. Though scientifically robust, these studies should be considered with some caution, as there is a lack of prospective observational data in the literature. In the absence of observational studies of children with autism-macrocephaly, it is not possible to conclude their phenotype will not broaden in adulthood to include cancer predisposition (Rodríguez-Escudero et al., 2011; Spinelli, Black, Berg, Eickholt, & Leslie, 2015).

On the basis of the lack of firm genotype–phenotype correlation, patients with a pathogenic or likely pathogenic PTEN variant, who present in childhood are advised to follow PHTS cancer surveillance guidelines as they get older.

4 | DIAGNOSTIC AND TESTING CRITERIA

Diagnostic criteria for PHTS have been published and are regularly updated by the National Comprehensive Cancer Network® (National Comprehensive Cancer Network® [NCCN®], 2019) (See Table 1). They are divided into major and minor criteria and various combinations can be used to qualify a diagnosis. The availability of these standardized criteria remains helpful for uniformly defining the condition, especially in the research setting. Substantial changes have happened with the removal of pathognomic criteria and more recently the removal of criteria that are common in the general population (uterine leiomyomata, fibrocystic disease of the breast) (Daly et al., 2017; Eng, 2000; Pilarski et al., 2013).

Gene-specific criteria for the interpretation of *PTEN* variants have been developed by the ClinGen *PTEN* Expert Panel (Mester et al., 2018). They offer a more bespoke approach to the American College of Medical Genetics variant interpretation guidelines and are a helpful tool for those involved in *PTEN* variant classification. Historic reports do not interpret variants with the same stringency as is now applied. In this review, we refer to variants when these are historically reported and not assessed against current pathogenicity criteria.

TABLE 1 Diagnostic criteria for PHTS. (Pilarski et al., 2013)

Major criteria
Breast cancer
Endometrial cancer (epithelial)
Thyroid cancer (follicular)
GI hamartomas (including ganglioneuromas, but excluding hyperplastic polyps; ≥3)
Lhermitte-Duclos disease (adult)
Macrocephaly (≥97th percentile: 58 cm for females, 60 cm for males)
Macular pigmentation of the glans penis
Multiple mucocutaneous lesions (any of the following):
• Multiple trichilemmomas (≥3, at least one biopsy proven)
• Acral keratosis (≥3 palmoplantar keratotic pits and/ or acral hyperkeratotic papules)
• Mucocutaneous neuromas (≥3)
• Oral papillomas (particularly on tongue and gingiva), multiple (≥3) OR biopsy proven OR dermatologist diagnosed
Minor criteria
Autism spectrum disorder
Colon cancer
Esophageal glycogenic acanthoses (≥3)
Lipomas (≥3)
Intellectual disability (IQ ≤75)
Renal cell carcinoma
Testicular lipomatosis
Thyroid cancer (papillary or follicular variant of papillary)
Thyroid structural lesions (e.g., adenoma, multinodular goiter)
Vascular anomalies (including multiple intracranial developmental venous anomalies)
Application of criteria
Operational diagnosis in an individual (either one of the following):
1. Three or more major criteria, but one must include macrocephaly, Lhermitte-Duclos disease, or GI hamartomas; or
2. Two major and three minor criteria
Operational diagnosis in a family where one individual meets revised *PTEN* hamartoma tumor syndrome clinical diagnostic criteria or has a *PTEN* pathogenic/likely pathogenic variant:
1. Any two major criteria with or without minor criteria; or
2. One major and two minor criteria; or
3. Three minor criteria

A useful clinical scoring system, (The Cleveland Clinic Score) based on prospective data, can estimate the likelihood of an underlying *PTEN* variant. It can be accessed online. Different criteria are used for adults and children. They are intended for use when no *PTEN* mutation has previously been identified in a family (M. H. Tan et al., 2011). See http://www.lerner.ccf.org/gmi/ccscore/ for more details. The pediatric criteria set a low threshold for testing, with macrocephaly and one other feature being sufficient. The adult criteria include phenotypes seen in the general population (e.g., uterine leiomyomata and fibrocystic disease of the breast), counting only as minor criteria, which are not a component of the current diagnostic criteria shown in Table 1. Recent progress in genetic testing has changed the utility of such diagnostic criteria for genetic conditions. Increasing numbers of children are diagnosed through broad testing in childhood (for example, though developmental delay/overgrowth panels or through exome sequencing). In this setting, having well-defined clinical criteria is important for supporting variant interpretation.

The childhood testing criteria for PHTS of macrocephaly with developmental delay and/or autism are not specific for *PTEN*. Therefore, it is to be anticipated that broad panel testing of children with suspected PHTS will reveal pathogenic variants in other genes with overlapping phenotypes. This is evidenced in a study in which a targeted analysis of cancer-related and non-cancer related genes on patients with a raised Cleveland clinic (CC) score who were wildtype for *PTEN* was performed. One pediatric patient with macrocephaly, developmental delay/autism had an *HRAS* copy number variant associated with Costello Syndrome (Yehia et al., 2018) In this situation, it is the role of a Clinical Geneticist to establish whether the clinical presentation and features are consistent with such an alternative diagnosis. Several studies have investigated individuals who meet criteria for CS or CS-like (using International Cowden Consortium criteria 2006, which are broader than current NCCN Clinical Practice Guidelines In Oncology [NCCN Guidelines®]) but do not harbor a pathogenic *PTEN* variant. These studies have identified *SDHD*, *SDHB*, *SDHC*, *KLLN* (methylation), *PIK3CA*, *AKT1*, *SEC23B*, and *EGFR* (adult with LD) as potential causes of CS and CS-like phenotypes in a proportion of patients, but no second gene has been consistently associated with PHTS. The majority of patients included in these studies had an adult cancer predisposition phenotype (i.e., CS/CS-like) (Bennett, Mester, & Eng, 2010; Colby et al., 2016; Ni et al., 2012, 2008; Orloff et al., 2013; Yehia et al., 2015).

5 | CLINICAL PRESENTATION OF PHTS IN CHILDREN

5.1 | Macrocephaly and growth

Macrocephaly (defined as an occipito-frontal circumference over 2*SD* above the mean) is an almost universal feature of PHTS and may be extremely pronounced; reported as averaging around +5 *SD* in childhood (Hansen-Kiss et al., 2017; Mester, Tilot, Rybicki, Frazier, & Eng, 2011). Antenatal presentation with macrocephaly detected on ultrasound scan, and presentations at birth and in infancy have been described (Busa et al., 2015; Kato et al., 2018; Lynch, Lynch, McMenamin, & Webb, 2009). A progressive increase in occipito-frontal head circumference is described and this alone may prompt referral for investigations (Balci et al., 2018; Vanderver et al., 2014).

This trend toward macrocephaly continues in adulthood, with the majority (94.4%) being reported with macrocephaly (Mester et al., 2011).

While PHTS is regarded as an overgrowth diagnosis, a finding of short stature should not detract from suspecting PHTS (Granados, Eng, & Diaz, 2013). Patients may show generally increased adiposity attributed to increased insulin sensitivity (Pal et al., 2012).

5.2 | Neurodevelopmental disorders including autistic spectrum disorders

Neurodevelopmental disorders are associated with PHTS. The original reports of BRRS included hypotonia and developmental delay and intellectual disability was included in the original report of CS. Many children diagnosed with PHTS will have presented with hypotonia and

large or increasing head size or a little later with delayed milestones. There is also some evidence that they may have abnormal musculature as discussed below. Intellectual disability and autism spectrum disorders are often reported. In the absence of prospective data, their prevalence remains unknown.

Motor delay is a common presenting symptom in young children with PHTS with hypotonia on examination (Busa et al., 2015; Lynch et al., 2009). Muscle biopsy has demonstrated a lipid storage myopathy in some patients (Diliberti, 1992). An account of the early reports of the conditions, now recognized to be component parts of PHTS, discusses a lipid myopathy with "the presence of intracellular lipid, large type 1 muscle fibers, and small type 2 fibers" on muscle histopathology. No evidence for *PTEN* pathogenic variants is provided. A report after recognition of the causal link with *PTEN* (Otto et al., 1999) discredits the previously reported association with long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency (Fryburg, Pelegano, Bennett, & Bebin, 1994). In a clinically convincing case of BRRS, variation in fiber size and mononuclear cell infiltration among the muscle bundles were observed, but serial section did not reveal any lipid deposition (Erkek et al., 2005).

A study of 18 children with autism spectrum disorder (ASD) and macrocephaly (+2.5*SD* – +8 *SD*)found a pathogenic variant in *PTEN* in 17% (Butler et al., 2005). The exact prevalence of *PTEN* mutations among people with ASD/DD is unknown as large scale data are lacking. In a study of 88 children with autism, only one variant that could be classified as pathogenic was identified (Buxbaum et al., 2007). A study of a mixed group of children with DD, ASD, and macrocephaly identified *PTEN* variants in children with DD (12.2%) and in children with ASD (8.3%) all of whom had macrocephaly emphasizing the tight association between these two features (Varga et al., 2009). Several other studies have confirmed the association of between *PTEN* variants and ASD and broader neurodevelopmental disorders in the presence of macrocephaly (Herman, Butter, et al., 2007; Herman et al., 2007; Hobert, Embacher, Mester, Frazier II, & Eng, 2014; Klein, Sharifi-Hannauer, & Martinez-Agosto, 2013; Marchese et al., 2014; McBride et al., 2010; Orrico et al., 2009). In the series, reported by Busch et al., the assessments suggested disruption of frontal circuits, with difficulties with retrieval based memory, measures of phonemic verbal fluency and fine manual dexterity and perseverative responding. The adults who performed at the lower end of the spectrum had had prior resection of cerebellar tumors (Busch et al., 2013). Another study provides further evidence of slower processing speeds and suggests that "behavioural treatment should focus on slow, repeated presentation of information to maximize learning, even in high functioning *PTEN*-ASD patients" (Frazier et al., 2015).

There are reports of neuropsychiatric diagnoses. In their retrospective review Hansen-kiss et al., reported a number of children as having diagnoses of attention deficit hyperactivity disorder (ADHD)/attention deficit disorder (ADD), anxiety, and obsessive compulsive disorder (OCD). Other diagnoses included bipolar disorder, social communication disorder and disruptive behavior disorder, oppositional defiant disorder and depression (see supplementary table in Hansen-kiss et al.) (Hansen-Kiss et al., 2017). In their article on white matter findings on MRI Balci et al., include a child with anxiety and severe OCD, a child with ADHD and symptoms of anxiety, and a child with ADHD and a psychotic episode (Balci et al., 2018).

While the presenting features in childhood to the medical profession are often developmental delay, intellectual disability and ASD (Hansen-Kiss et al., 2017) a study demonstrated average intelligence quotients (IQ mean 103 with a wide range of 65 to 135) (Busch et al., 2013). In series of patients, intellectual disability was reported in 12–17% (Hanssen & Fryns, 1995; Lachlan et al., 2007; Pilarski, Stephens, Noss, Fisher, & Prior, 2011). Early reports described a high (50%) rate of motor and speech delays, but normal intelligence in adulthood (Parisi et al., 2001).

In summary, initial speech and motor delay neither preclude normal intellectual development, nor predict for significant physical disability. Hence, for young children with low tone and delayed speech and language development, cautious optimism is appropriate. For some patients, these presenting features will be the earliest signs of intellectual disability or autistic spectrum disorder and they will need ongoing pediatric follow-up and appropriate therapy input. Some people do not come to early medical attention, but are diagnosed in adulthood and so it is assumed that early development can be without significant difficulties. However, some will have had medical and developmental investigations, but no unifying diagnosis made until adulthood. Neuropsychiatric diagnoses may be a component of PHTS and psychological assessments are reported to reveal memory and processing speed deficits, but further evidence is required.

5.3 | MRI imaging including Lhermitte-Duclos disease

There is great variability in MRI brain appearances in PHTS. Some individuals with PHTS have normal MRI appearances though the spectrum can include a variety of white matter changes, cortical malformations, hemimegalencephaly and benign growths. In this section, we review case series and reports of neuroimaging in PHTS. We include reports of Lhermitte-Duclos Disease which is uncommon in childhood.

A report by Lok et al. included 20 CS patients in its analysis. The 10/20 patients had *PTEN* variants and normal MRI brain appearances, though details/pathogenicity of the *PTEN* variants were not supplied (Lok et al., 2005).

A series of 23 patients with pathogenic *PTEN* variants, macrocephaly,-and developmental delay, with or without autism, all ascertained because of white matter abnormalities, which were multifocal and static is reported. Enlarged perivascular spaces were also recognized (Vanderver et al., 2014) (See Figure 1a). In a group of 20 patients, ascertained through dermatology practice, who were asymptomatic for neurological disease, one was found to have nonspecific white matter abnormalities (Lok et al., 2005).

In a MRI brain scan series of seven children with BRRS phenotype; all had macrocephaly with CSF signal intensity (hyperintense on T2 and hypointense on FLAIR) and white matter cysts in the parietal lobes (Bhargava, Au Yong, & Leonard, 2014).

A more recent study provides further evidence for these MRI appearances, and remarks on the highly variable neuropsychiatric and neurological features, ranging from normal to severely disabling with focal neurological findings, but with a lack of correlations for the severity of the neurology with the MRI findings (Balci et al., 2018). In a case–control study (*PTEN*-ASD vs. idiopathic ASD vs. Idiopathic ASD-macrocephaly) overgrown, but poorly developed white matter with multiple hypointensities was observed in the MRI scans of *PTEN*-ASD patients. In contrast to the Balci et al.'s article, the authors comment that the slow processing speed and large deficits in working memory observed in their patients were "consistent with prominent white matter abnormalities" (Frazier et al., 2015).

Cortical malformations are reported in patients with *PTEN* variants (Guerrini & Dobyns, 2014). The macrocephaly in the majority of PHTS patients is symmetrical; however, there are reports of hemimegalencephaly with cortical malformations in patients (Ghusayni, Sachdev, Gallentine, Mikati, & McDonald, 2018; Merks, 2003). Elia et al. reported that a 4-month-old child, who presented with seizures had, "a dysplastic cleft surrounded by thickened and polymicrogyric cortex in the right sylvian region; on the same side globally reduced myelination and periventricular gliosis were recognizable" (Elia et al., 2012). Another case report describes a girl presenting with focal epilepsy, found to have abnormalities of the right occipital lobe, described as pachygyria with hyperplastic white matter and disorganization of the gray and white matter and alternatively described by the authors as right megalencephaly (Cheung, Lam, Chan, Siu, & Yong, 2014).

Lhermitte–Duclos disease (LDD) is a benign dysplastic gangliocytoma of the cerebellum, usually affecting one hemisphere. It presents with ataxia, nystagmus or symptoms of raised intracranial pressure (Lhermitte & Duclos, 1920; Ma, Jia, Chen, & Jia, 2019). Even without recognized evidence of other features of PHTS, there is a high chance of finding a pathogenic *PTEN* variant in an adult diagnosed with LDD (Zhou et al., 2003). When diagnosed in adulthood it is a major diagnostic criterion for PHTS (Daly et al., 2017; National Comprehensive Cancer Network® [NCCN®], 2019).

The incidence of LDD in PHTS is unknown with the majority of reported patients presenting with LDD as the presenting feature of PHTS, or the neurological symptoms being recognized in a person with PHTS, thus making any estimate of the incidence skewed. In a series of MRI scans 20 PHTS patients who were neurologically asymptomatic (age range 9 to 72 years) three were found to have LDD (Lok et al., 2005).

LDD can be a challenge to diagnose radiologically in children due to the absence of the typical "tiger stripe" appearance on T2-weighted MRI images (Ma et al., 2019) (See Figure 1b). Children may not show other features of PHTS when assessed clinically and so will be reported to have LDD as an isolated finding (Robinson & Cohen, 2006). In series of children with PHTS and in whom neuroradiology was performed, no cases of LDD are reported (Bhargava et al., 2014; Frazier et al., 2015; Hansen-Kiss et al., 2017; Vanderver et al., 2014). None of the three children in the Zhou et al. series had a germline pathogenic variant (Zhou et al., 2003). In contrast, in their 2006 review Robertson and Cohen relate 14 cases in the literature of LDD presenting in childhood of which 3 had a diagnosis of CS made clinically; these include the 12-year-old with LDD and a clinical and family history consistent with CS (Perez-Nunez et al., 2004) and their own previously reported patients (Robinson & Cohen, 2000). An 11-year-old with LDD is reported to have a clinical diagnosis of CS (Jiang et al., 2017). Another report discussed three children with LDD who were wild type for PTEN and did not develop PHTS features during follow up (Mori et al., 2003). An infant with a pathogenic PTEN variant reported with cortical dysplasia and epilepsy had an incidental finding of LDD, which later enlarged resulting in the descent of the cerebellar tonsils and necessitating an external shunting procedure followed by surgical removal of the tumor (Elia et al., 2012). There is another report of a child presenting with progressive, headaches, and loss of balance with LDD (Sutphen et al., 1999). Three adolescents are reported with pathogenic PTEN variants and LDD (Wang et al., 2017).

While there are limited data, there are reports of LDD as a component of PHTS in childhood and so its occurrence should prompt consideration of PTEN testing. As genetic testing becomes increasingly mainstream, reports of LDD in childhood may emerge through clinical reports and patient registry data.

Treatment of LDD is surgical, although conservative management is also adopted where symptoms are minimal. The tumor has indistinct margins making total resection challenging, if not impossible.

There is a report of a child with LDD unamenable to surgical removal, treated with rapamycin with a good response to treatment (Zak, Ledbetter, & Maertens, 2017). She was not reported to have been tested for germline PTEN pathogenic variants.

There are reports of tonsillar descent without LDD, with incidence higher in the general population, but it remains unclear if this is a true association (Dhamija et al., 2018; Saletti et al., 2017).

There are reports of meningiomas, but these have not formed a component of diagnostic criteria (Busch et al., 2013; Dhamija et al., 2018; Liaw et al., 1997; Lok et al., 2005; Yakubov et al., 2016).

In summary, PHTS should be a differential diagnosis in children with nonspecific white matter changes detected in the context of macrocephaly and developmental delay. There are reports of benign tumors, although these are not common in children. Given the likely need for general anesthesia, and the fact that most MRI changes will not be actionable, we do not advocate for routine neuroimaging solely based on a new PHTS diagnosis. This should be reserved for symptomatic children or those with abnormal neurological examinations.

5.4 | Facial, skin, and mucosal features

Unlike other macrocephaly-developmental disorders, PHTS does not have a striking facial gestalt. Patients may have a prominent or bossed forehead with depression of the nasal bridge or midface (Butler et al., 2005; Herman, Butter, et al., 2007). A recent article illustrates in addition to these features, horizontal eyebrows, and dolichocephaly (Kato et al., 2018).

The original reports of CS focus on the recognizable dermatological characteristics in adults. Trichilemmomas are hamartomatous growths of the outer sheath of the hair follicle. They can be found

elsewhere on the body though they are typically seen on the face and may be concentrated around the orifices (Nosé, 2016) (See Figure 2c). It is not possible to accurately distinguish these from other growths of the hair follicles through clinical examination, so they must be biopsied to confirm the histological diagnosis (Daly et al., 2017). This may pose practical difficulties in children or in patients with a learning disability or autism. A current utility for skin biopsies in PHTS may lie in providing additional clinical support for a variant of uncertain significance.

Acral keratoses have a verrucous appearance and occur mostly on the extensor or palmoplantar surface of the extremities. Pitted lesions are also seen (Salem & Steck, 1983; Starink et al., 1986) (See Figure 2a).

The tongue may have an abnormal appearance with papillomas or a scrotal appearance (Figure 2b). The palate may be high-arched (Lloyd & Dennis, 1963; Parisi et al., 2001; Salem & Steck, 1983) (Figure 3c). Papilloma may be found on the lips, gums, or tongue and are considered a major diagnostic criterion (Pilarski et al., 2013). Mucosal neuromas may be present in the mouth and may cause difficulties with dental hygiene (Figure 2b). They are a common feature of PHTS and may be present in young patients (Starink et al., 1986). Neuromas have also been described in the skin (Ferran, Bussaglia, Lazaro, Matias-Guiu, & Pujol, 2008).

The features of PHTS that affect the skin and mucosa may not be present in children, given their age-related penetrance (Pilarski et al., 2011; M. H. Tan et al., 2011). With meticulous examination, and particularly in later childhood and adolescence, these features may be recognized (Lachlan et al., 2007). Where possible, examination of the parents' skin and oral cavity should also be undertaken.

Inspection of the genitalia may reveal pigmented macules on the glans penis; unlike the other skin findings this is common in the childhood presentation and has been in reported in children as young as 1 year (Dvir et al., 1988; Smpokou, Fox, & Tan, 2015; W. H. Tan et al., 2007).

Malignant melanoma is described, with an incidence of 2–6%, and an average age of onset in the forties. The youngest described patient was 2 years of age (Bubien et al., 2013; Ngeow & Eng, 2015; M.-H. Tan et al., 2012).

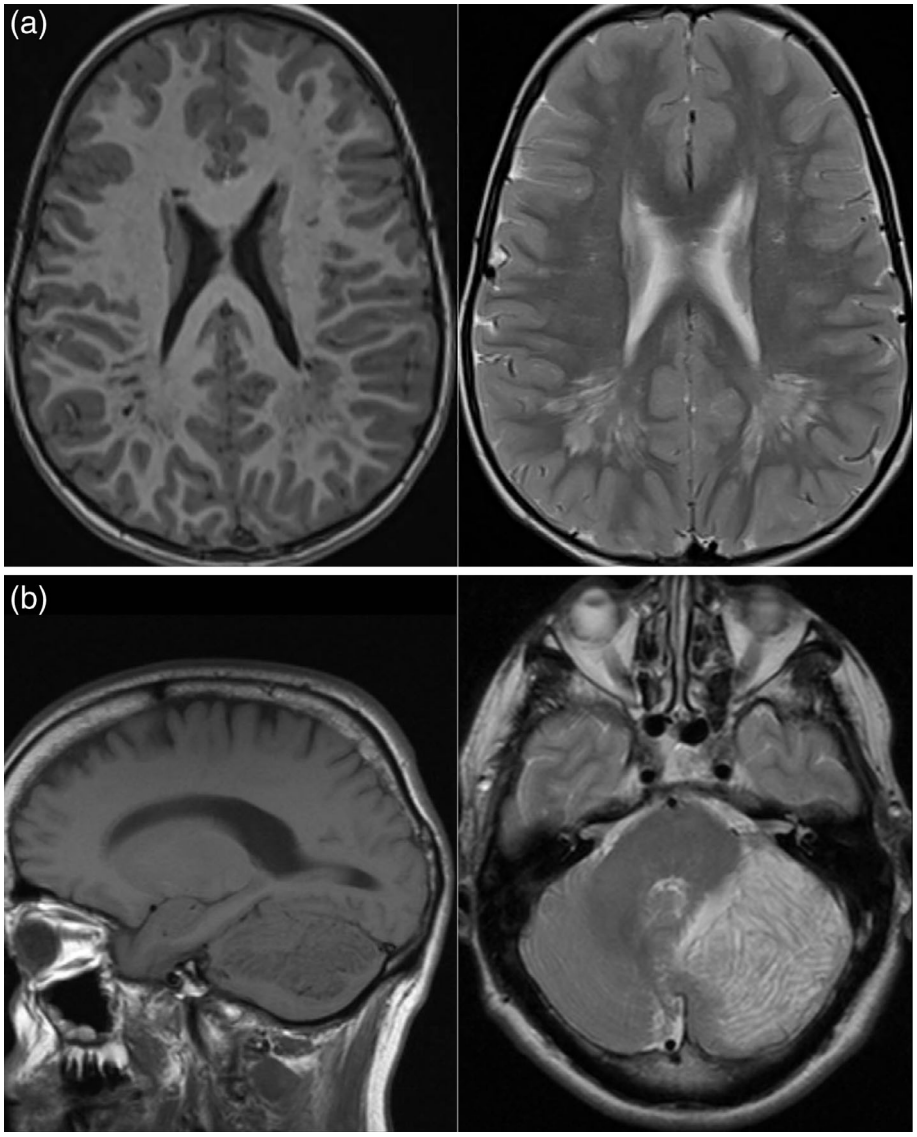

FIGURE 1 MRI features of PHTS. (a) Includes axial T1- and T2-weighted MRI images demonstrating prominent perivascular spaces, which radiate out from the ventricular margin. (b) Includes sagittal T1 and axial T2 MRI images showing abnormal tissue in the left cerebellar hemisphere with a characteristic tigroid appearance and apparently preserved cerebellar folia

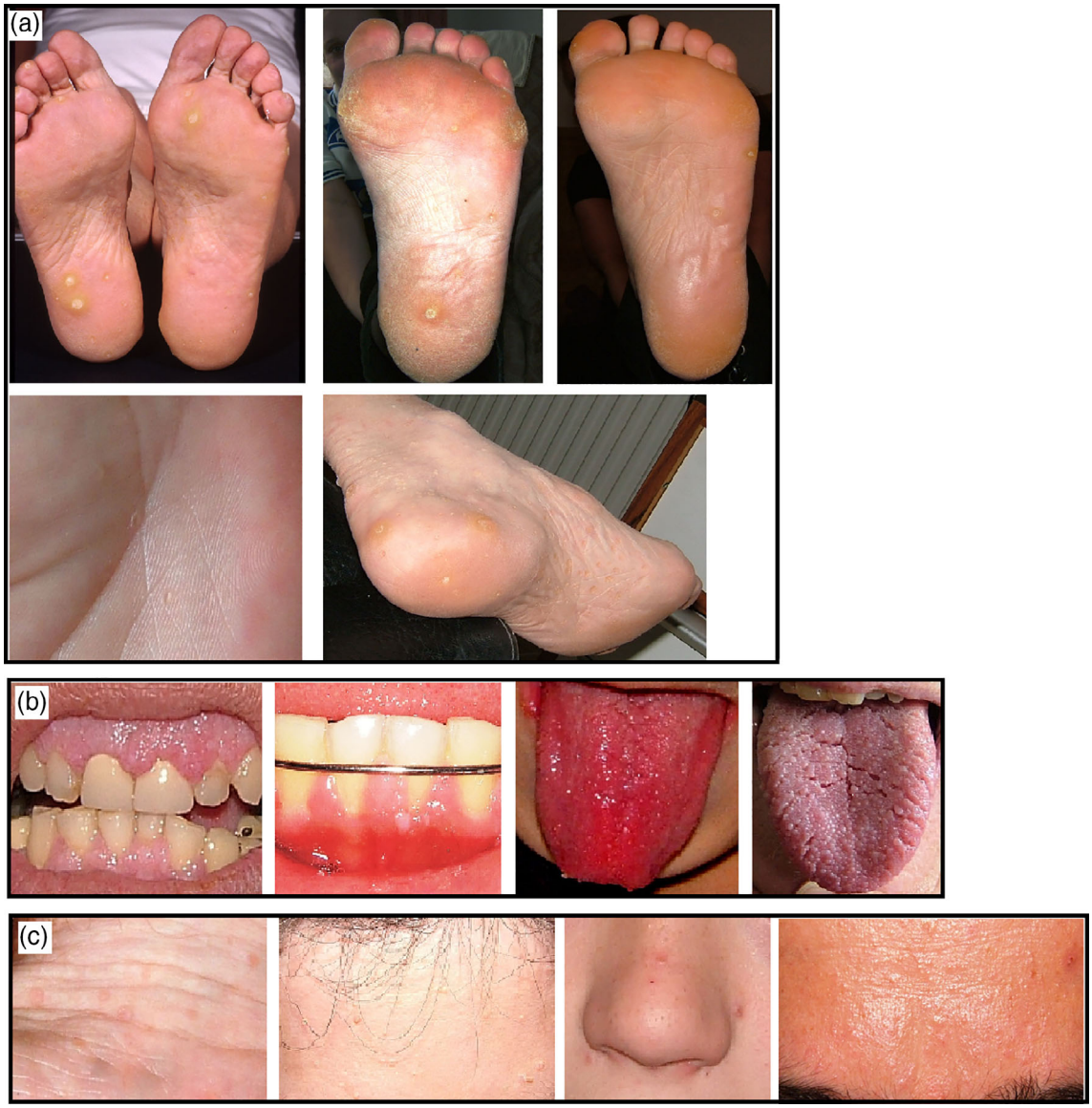

FIGURE 2 Mucocutaneous manifestations of PHTS. (a) Shows plantar and palmar keratoses. Some are hyperkeratotic and may resemble viral verrucous lesions. Note that pitted lesions may be subtle, such as in the palmar image shown. (b) Shows oral mucosal features. Gingival papillomas and neuromas may encroach on the dentition and cause difficulty with dental hygiene. Papillomatosis of the tongue is also seen. (c) Shows Trichilemmomas. These are often found on the face. They may resemble other lesions (e.g., comedones/acne) and biopsy is be required to confirm the histological diagnosis

5.5 | Thyroid

A wide variety of thyroid disorders have been described in childhood in PHTS. These include benign and malignant lesions and autoimmune conditions.

Benign disorders include nodular goiter, single, or multiple follicular adenomas, autoimmune thyroid disease including Hashimoto's thyroiditis and lymphocytic thyroiditis (Laury, Bongiovanni, Tille, Kozakewich, & Nosé, 2011; Plamper et al., 2018). Benign thyroid lesions have been described as young as 5 years and may be present on initial screening ultrasound (Smpokou et al., 2015). A recent case report highlights the need for thyroid surveillance, for risk of respiratory compromise secondary to compression from a multinodular goiter, detectable on clinical examination (Tosur, Brandt, Athanassaki, & Rednam, 2018). Screening guidance focusses on malignancy risks, but the clinician should be alert to the possibility of thyroid dysfunction (Hansen-Kiss et al., 2017).

Multicentric, bilateral, adenomatous nodules in a background of lymphocytic thyroiditis with benign and/or malignant follicular cell-derived neoplasms are described as characteristic and should alert clinicians to a diagnosis of PHTS (Cameselle-Teijeiro et al., 2015; Harach, Soubeyran, Brown, Bonneau, & Longy, 1999; Laury et al., 2011; J. R. Smith et al., 2011). These features could also be helpful to note if a *PTEN* variant of uncertain significance is identified.

Thyroid nodules including adenomas and multinodular goiter are common in adults with PHTS. The risk of thyroid cancer in adulthood

is reported to be increased above the general population risks. Older studies gave a risk of 3–10% (Pilarski, 2009). More recent studies report higher lifetime risks, of 35–38% (Bubien et al., 2013; Ngeow et al., 2011; M.H. Tan et al., 2012).

Several case series have described thyroid cancer in early childhood. The earliest presentations include a papillary microcarcinoma in a 6-year-old and three cases of thyroid cancer in 7-year-olds (Laury et al., 2011; Ngeow et al., 2011; Plamper et al., 2018; J. R. Smith et al., 2011; Smpokou et al., 2015). Apart from follicular and papillary microcarcinoma, classical papillary and Hürthle cell cancers have also been described in children (Ngeow et al., 2011). PTEN testing should be considered in children presenting with thyroid cancer, especially where macrocephaly co-exists (Ngeow et al., 2011; Smpokou et al., 2015).

Even though current NCCN guidance recommend annual thyroid ultrasound scan from diagnosis, including in childhood, (National Comprehensive Cancer Network® [NCCN®], 2019) there is no evidence base aside from these reports of very early thyroid cancer diagnoses (Laury et al., 2011; Ngeow et al., 2011; Plamper et al., 2018; J. R. Smith et al., 2011; Smpokou et al., 2015). In healthcare settings where a clear evidence-base is required for funding, this guidance is unlikely to be implementable outside of a clinical study. The UK Cancer Genetics Group advocate starting screening at age 16, tailored to family history. It may be offered earlier depending on an informed discussion with the family.

As in other diseases with a tumor risk in childhood, there is no case–control series to demonstrate clinical outcomes nor cost–benefit (Kalish & Deardorff, 2016). Psychological impact on families is another important consideration (Duffy, Grand, Zelley, & Kalish, 2018; Gopie, Vasen, & Tibben, 2012), but is not studied in PHTS. The American thyroid association guidelines task force on pediatric thyroid cancer did not endorse the NCCN guidance, recommending annual examination, with follow up of clinical abnormalities, "in a centre of excellence so that appropriate evaluation, follow-up, genetic counseling, and/or treatment can be undertaken without subjecting patients and families to unwarranted and aggressive therapy."(Francis et al., 2015).

The high sensitivity of ultrasonography means that small nodules of uncertain clinical significance are frequently identified. The most accurate test in nodule evaluation is fine needle aspiration (FNA), but it is not fully sensitive (Dean & Gharib, 2008). As it can be difficult to out rule cancer based on imaging and FNA alone, many patients with suspicious lesions on ultrasound will have a thyroidectomy. Plamper et al. argue the role of thyroidectomy for suspicious lesions over FNA. They note FNA has many shortcomings including the need general for anesthesia in children with PHTS, its limited role when there are multiple suspicious lesions (common in PHTS), and its inability to distinguish follicular adenomas from follicular carcinomas on cytology (Plamper et al., 2018). Furthermore, if a partial thyroidectomy is performed a second pathology may develop in the remaining tissue requiring more invasive surgery (J. R. Smith et al., 2011). Thyroidectomy is not without risks, and such an approach will mean the removal of a certain amount of non-cancerous thyroids, as in the Plamper case series (Schultz et al., 2017). Decision-making around screening and thyroid surgery should be tailored based on discussion including issues such as family history, tolerability of procedures, and subsequent ongoing treatment for an individual (e.g., in children or young adults with neurodevelopmental disorders) (Milas et al., 2012; Tosur et al., 2018).

5.6 | Vascular and lipomatous lesions

Lipomas are a key diagnostic component of BRRS. The presence of three or more lipomas counts as a minor criterion in the revised PHTS diagnostic criteria, as the presence of multiple lipomas in the general population is rare (Daly et al., 2017; Pilarski et al., 2013). They also count as a criterion in the Pediatric Cleveland clinic score, although the number is not specified (M. H. Tan et al., 2011). Lipomas are a rare soft tissue tumor in childhood in the general population and can be the presenting complaint bringing children with PHTS to medical attention (Buisson et al., 2006) (See Figure 3).

Testicular lipomatosis is described in adult males with PHTS. Multiple hyperechoic bilateral well-defined lesions in the testes, which are usually not palpable on examination. The reported patients have come to medical attention due to testicular pain, secondary to orchitis (Alnajjar, Sahai, Keane, & Gordon, 2011) and epididymal cyst (Lindsay, Boardman, & Farrell, 2003). The lipomatosis appears to be an incidental finding. Case reports of testicular lipomas unrelated to PHTS are rare and describe solitary lesions. A study of eight males found no association with infertility. There is no evidence that these lesions predispose to malignancy (Woodhouse, Delahunt, English, Fraser, & Ferguson, 2005). The youngest patient described was 16 years old.

Vascular anomalies are classified broadly into vascular tumors (such as haemangiomas) and vascular malformations (including venous malformations, and AVM) (International Society for the Study of Vascular Anomalies, 2018). A wide range of terms has been used to describe the anomalies seen in PHTS (See the discussion section of Kurek et al. for a comprehensive review of historical descriptions [Kurek et al., 2012]). In the intervening years since they were first described, the terminology for vascular anomalies has evolved and most historic publications lack sufficient histopathological and radiological details for accurate re-classification. High and low flow vascular malformations are seen in PHTS with a preponderance of high flow lesions (Johnson & Navarro, 2017; W. H. Tan et al., 2007). A vascular anomaly in a macrocephalic child is sufficient to prompt PTEN testing (M. H. Tan et al., 2011).

The term *PTEN* hamartoma of soft tissue (PHOST) has been suggested to describe a complex characteristic overgrowth seen in PHTS, although these may represent benign neoplasms as opposed to true hamartomas. PHOSTs may contain adipocytic and fibrous tissues, mixed vascular elements, lymphoid follicles, bone, or hypertrophic nerves (Kurek et al., 2012). They have not yet been classified as either vascular tumors or malformations (International Society for the Study of Vascular Anomalies, 2018). PHOSTs are predominantly intramuscular lesions and tend to occur in the lower limbs in children and young people. They often present with swelling and pain but may even be clinically apparent from birth (Kurek et al., 2012).

Lesions may be identified clinically with discoloration of the overlying skin, swelling, or a history of pain. A case series of children with pathogenic *PTEN* variants demonstrated vascular lesions in over half of the patients, though some were recruited through a vascular anomaly clinic potentially causing some over-representation. Ectopic fat was associated with many of the vascular lesions and in one case seen in isolation in the abdomen (W. H. Tan et al., 2007).

AVM are described in many sites, including viscera, brain, neck, face, skin, intestines, pelvis, extremities, and spine. AVMs may be fed from a variety of vessels from major arteries to capillaries (Busa et al., 2015; Inukai et al., 2018; W. H. Tan et al., 2007; Turnbull, Humeniuk, Stein, & Suthers, 2005; Weary et al., 1972).

Vascular anomalies may involve the CNS. Spinal haemangiomas and cerebral and cerebellar vascular malformations have been observed (Gujrati, Thomas, Zelby, Jensen, & Lee, 1998; Kurek et al., 2012; Lok et al., 2005; W. H. Tan et al., 2007).

In summary, a variety of vascular and lipomatous lesions are described in PHTS, from simple lipomas to arteriovenous malformations and complex mixed-tissue lesions. Some lesions such as lipomas and testicular lipomatosis tend to be asymptomatic or of cosmetic concern only, though knowledge of them is useful when trying to establish a diagnosis. Other lesions, such as complex growths in the limbs, can cause significant symptoms and can be challenging managing; these should be assessed for during the child's annual clinical review.

5.7 | Lymphoid tissues, autoimmunity, and immune dysfunction

Enlargement of the tonsillar tissue due to lymphoid hyperplasia is described in PHTS (Dvir et al., 1988; Erkek et al., 2005; Heindl et al., 2012; Kimura, Miwa, & Furukawa, 1992; Omoyinmi et al., 2017; Piccione et al., 2013). A child is reported with a history of snoring and demonstrable sleep apnoea, which responded to adenotonsillectomy (Sharma, Petty, & Lesperance, 2007). Airway obstruction has been reported due to papillomas in the upper airway (Abdul Latiff et al., 2010; Lachlan et al., 2007; Omote, Kawamata, Imaizumi, & Namiki, 1999; Sharma et al., 2007).

Lymphoid hyperplasia can also be seen in the thymus, where it has been reported to cause airway obstruction (Heindl et al., 2012; Schmid et al., 2014) and throughout the gastrointestinal tract when presentation can be with anemia (Boccone et al., 2007; Heindl et al., 2012). Reports of immune dysregulation and autoimmunity include Hashimoto's thyroiditis, hemolytic anemia, vasculitis colitis (Heindl et al., 2012; D. J. Marsh et al., 1999; Mauro, Omoyinmi, Sebire, Barnicoat, & Brogan, 2017). Abnormalities of B-cell homeostasis are reported, without evidence of immunodeficiency (Heindl et al., 2012).

Some patients with immunodeficiency attributed to PHTS have been reported. These include hypogammaglobulinemia and CD4+ T-cell lymphopenia (Browning, Chandra, Carbonaro, Okkenhaug, & Barwell, 2015) and deficiency of T-lymphocyte function, with recurrent cellulitis and abscess formation, and the eventual development of acute myelogenous leukemia (Ruschak, Kauh, & Luscombe, 1981) A child is described with a declining response to Haemophilus B and pneumococcal vaccines (Browning et al., 2015).

Immune dysregulation is not in itself a component of the PHTS diagnostic criteria (excepting Hashimoto's thyroiditis, which counts toward scoring in the Cleveland Clinic scoring method) (M. H. Tan et al., 2011). Immune dysregulation in PHTS is gaining attention, not only in terms of the clinical manifestations but also with a view to possible future treatments of malignancies (Eissing et al., 2019; Nunes-Santos, Uzel, & Rosenzweig, 2019).

5.8 | Gastrointestinal manifestations

Polyposis is one of the most penetrant features of PHTS (Heald et al., 2010). Polyps may be found throughout the bowel from the stomach to colon and histology can be varied including hamartomatous polyps, hyperplastic polyps, adenomas, inflammatory polyps, and ganglioneuromas (Heald et al., 2010). Polyps may present acutely with rectal bleeding due to intussusception (Kethman, Rao, Devereaux, Ouellet, & Kin, 2017).

Juvenile polyposis of infancy (JPI) is an early onset, life-limiting condition presenting with growth failure, anemia, recurrent gastrointestinal bleeding, diarrhea, rectal prolapse, intussusception, protein-losing enteropathy, and malnutrition, caused by deletions of chromosome 10q23, encompassing both *PTEN* and another tumor suppressor gene, *BMPR1A*. The severity of this condition was hypothesized to be due to the loss of these two tumor suppressors, which function in two different, but cooperative, pathways (Delnatte et al., 2006). Further case series demonstrated patients with 10q23 deletions presenting with more varied phenotypes. These included later onset of polyposis and generalized PTHS features such as macrocephaly, intellectual disability, hypotonia, and cancer predisposition (Menko et al., 2008; Salviati et al., 2006). Cardiac defects are also described and a patient with infantile polyposis and bilateral mucinous cystadenoma of the ovaries has also been published (Babovic et al., 2010; Menko et al., 2008). Patients have also been described with mosaicism for the deletion, and paracentric inversion of 10q with deletion of 10p (Lindhurst et al., 2011; Vargas-González et al., 2010).

An upper endoscopy may reveal glycogenic acanthosis of the esophagus (Levi et al., 2011; McGarrity et al., 2003). These lesions now make up part of the diagnostic criteria. Glycogenic acanthosis has also been described on the gingiva (Nishizawa et al., 2009). We have not found reports of glycogenic acanthosis in childhood. Acanthosis nigricans is reported (Erkek et al., 2005; Fargnoli et al., 1996; Ruvalcaba et al., 1980) (Figure 3e). While adiposity alongside this feature would usually raise clinical suspicion of a diagnosis of type II diabetes, PHTS patients conversely have higher insulin sensitivity than controls (Pal et al., 2012).

5.9 | Rare associations

PTEN variants have been found in some patients reported as having Proteus Syndrome (PS) and PS-like phenotypes (X.-P. Zhou et al., 2000; X. P. Zhou et al., 2001). These descriptions resemble the more recent descriptions of PHOST (Kurek et al., 2012) (See vascular and

lipomatous abnormalities section above). Mosaic pathogenic variation is described as an explanation for these phenotypes (Nathan, Keppler-Noreuil, Biesecker, Moss, & Darling, 2017). A patient with an epidermal nevus (Loffeld et al., 2006) and two further patients with SOLAMEN syndrome (Segmental overgrowth, lipomatosis, arteriovenous malformation and epidermal nevus) (Caux et al., 2007) are reported with loss of heterozygosity for an inherited *PTEN* variant. The PHOST may represent the same phenomenon (Kurek et al., 2012; Nathan et al., 2017).

PS is a rare overgrowth disorder characterized by severe progressive overgrowth of tissues with connective tissue and epidermal naevi, hyperostosis, and vascular malformations. PS is now known to be caused by somatic mosaic mutations in *AKT1* (Lindhurst et al., 2011). Several studies have not identified *PTEN* mutations in patients with classic Proteus, differentiated by relentless asymmetric growth of bone and the presence of cerebriform connective tissue nevus (Barker, 2002; Biesecker, Rosenberg, Vacha, Turner, & Cohen, 2001; Cohen, Turner, & Biesecker, 2003; Thiffault, Schwartz, Der Kaloustian, & Foulkes, 2004; Turner, Cohen, & Biesecker, 2004).

A rare presentation is described with similarities to the VATER-hydrocephalus phenotype, with tracheoesophageal fistula, pre-axial polydactyly and 13 sets of ribs (Reardon, 2002). Polydactyly is reported (Buxbaum et al., 2007; Delatycki, Danks, Churchyard, & Zhou, 2003). It is also of note that trachea-oesophageal atresia was also present in the youngest sibling reported by Riley and Smith (Riley & Smith, 1960).

Linear sebaceous naevi were reported in the child initially clinically diagnosed with Jadassohn nevus sebaceou (Merks, 2003).

Descriptions of ocular abnormalities are rare. Posterior subcapsular congenital cataract (Boccone, Dessì, Serra, Zibordi, & Loudianos, 2008) and prominent Schwalbe's lines, prominent corneal nerves, and pseudo papilloedema are described in early reports (Diliberti, 1998; Dvir et al., 1988; Riley & Smith, 1960). A recent article describes intracranial hypertension in two siblings with PHTS. Both patients were noted to have swollen optic disks at a very young age (at 1.5 years and 10 months). MRI of the brain was normal in both patients apart from thickening of the optic nerves in one patient and signal abnormality of the optic nerves in the second. Patients responded to medical treatment with acetazolamide but one relapsed upon discontinuation of treatment and interestingly was noted to have worsening of his autistic symptoms at this time. Though this case report cannot establish PHTS as the definitive cause of familial intracranial hypertension the report is worthy of note if faced with a patient with new-onset headaches or behavioral change (Hady-Cohen et al., 2019). Khana et al. reported a 15-year-old boy who was diagnosed with a retinal astrocytoma. He was diagnosed with PTHS after passing a bowel polyp and was recognized to have other systemic features of PHTS. Eye screening was performed to assess for cataracts as he also suffered from Myotonic Dystrophy. Molecular investigations revealed a whole gene deletion of *PTEN* and *KLLN* (Khanna et al., 2019). There are case reports of cataracts (Boccone et al., 2008; C. Marchese et al., 2003).

Hearing loss, scoliosis, multiple café-au-lait patches are reported and in addition pectus excavatum and joint hypermobility (Erkek et al., 2005; Hansen-Kiss et al., 2017; C. Marchese et al., 2003; Parisi et al., 2001; Piccione et al., 2013).

Hypoglycaemia is reported along with testicular microlithiasis, short stature and a coagulopathy (Granados et al., 2013). A further report of testicular microlithiasis is accompanied by precocious puberty (Ozsu, Sen, & Ceylaner, 2018). Another report describes a boy with a balanced translocation of 10q and 13q, including the *PTEN* gene, precocious puberty, a convincing clinical BRRS phenotype, and a chorionic gonadotropin-secreting tumor (Ahmed et al., 1999). An 11-year-old boy with a renal cell carcinoma, a 16-year-old girl with a unilateral granulosa cell tumor of the ovary, and a 16-year-old boy with a colonic ganglioneuroma are reported. Molecular details were not supplied (Smpokou et al., 2015).

For all these reports, it is important to acknowledge that no clear association can be drawn with the *PTEN* variants reported, however, as with all rare diseases, the phenotype is only expanded with case reports or detailed and long term follow up studies.

6 | TREATMENT WITH INHIBITORS OF THE MTOR PATHWAY IN PHTS

PTEN is involved in downregulating the AKT/mTOR pathway. When not functioning properly it fails to dephosphorylate PIP3 (phosphatidylinositol 3,4,5-trisphosphate) to PIP2 (phosphatidylinositol 3,4,5-diphosphate) and hence fails to inhibit AKT. This, in turn, leads to phosphorylation of downstream molecules resulting in decreased apoptosis and increased cell growth. See Mester et al. for a comprehensive review of the pathway as it applies to PHTS (J. Mester & Eng, 2013) (See Figure 4).

Several studies have shown that loss of PTEN function in animal models causes PHTS-type symptoms, which are ameliorated by mTOR inhibitor administration. For example, a mouse model with *PTEN*-null neurones in the hippocampus and cerebral cortex has been shown to develop abnormal behavior, macrocephaly, seizures, and hypertrophic neurones (Kwon et al., 2006; Ogawa et al., 2007). This was associated with activation of the PI3K/AKT/mTOR pathway (Kwon et al., 2006). A later study demonstrated that administration the mTOR inhibitor rapamycin reversed neuronal hypertrophy and improved abnormal mouse behaviors (J. Zhou et al., 2009).

Mice with tissue-specific deletion of *PTEN* and PTEN+/− mice have been shown to develop PHTS-type tumors (Backman et al., 2004; Stambolic et al., 2000). In another proof of concept study, mice with deletion of *PTEN* in epithelial cells treated with rapamycin had regression of PHTS-type mucocutaneous features. Rapamycin also prevented the development of PHTS-type lesions when given prophylactically (Squarize, Castilho, & Gutkind, 2008). Inhibitors of the mTOR pathway have been used as a treatment for PHTS and JPS, but these have been on a case-by-case basis for patients with extreme phenotypes (Iacobas et al., 2011; Schmid et al., 2014). Initial studies in adults with PHTS have suggested oral sirolimus may be tolerated and effective in treating cutaneous and gastrointestinal features, improving cerebellar function and decreasing mTOR signaling, but careful monitoring for side effects

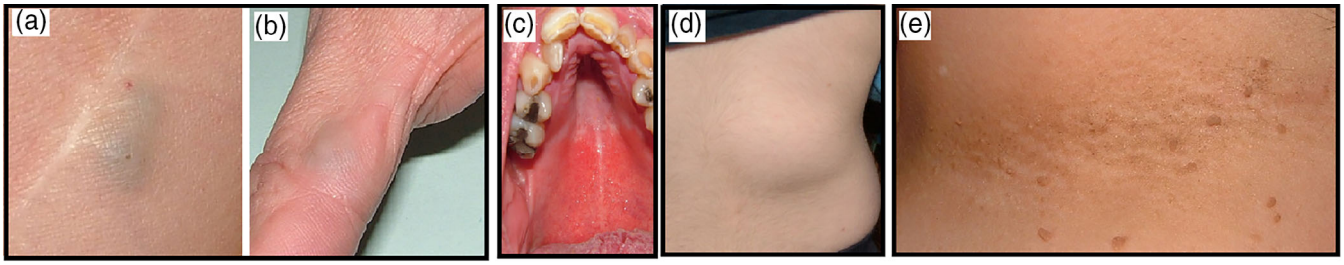

FIGURE 3 Clinical features of PHTS. (a and b) Shows lipomas on a wrist and a digit; note the blue discoloration due to vascular involvement. Also note the wrist scar in image (a) indicating re-growth following previous surgical removal. Images (c) demonstrate a high and narrow palate, (d) show a large lipoma in the right flank. (e) Show acanthosis nigricans on a patient's neck

including renal function, hypercholesterolemia, hypophosphatemia, and lymphopenia is essential (Komiya et al., 2013).

A double-blinded study is currently underway in the US investigating the safety and effectiveness of Everolimus on neurocognition (See https://clinicaltrials.gov/ct2/show/NCT02991807?cond=PTEN+Hamartoma+Tumor+Syndrome&rank=2).

7 | DIFFERENTIAL DIAGNOSIS AND APPROACH TO GENETIC TESTING

In childhood, the differential diagnosis for PHTS encompasses overgrowth syndromes with developmental delay, hypotonia, and intellectual disability. The macrocephaly is an important differentiating feature, with presentation prior to or in early childhood, sometimes with exponential growth over the first years of life, resulting in investigations for hydrocephalus. There are limited data on height but tall stature, are not an essential feature of the condition. The emergence of dermatological and mucosal features can help to differentiate, although the pitted keratoses can be mistaken for plantar pits observed in Gorlin (OMIM #109400) syndrome. There is no gestalt to the facial characteristics in PHTS and so it may be that the absence of the characteristic facial characteristics of other overgrowth syndromes (e.g., Soto) is a pointer toward PHTS.

For children who have clinical features consistent with PHTS (e.g., autism-macrocephaly phenotype), yet have negative *PTEN* testing results (sequencing, dosage and promotor analysis), a broader approach to testing (e.g., with array comparative genomic hybridisation/exome/genome sequencing or a panel approach [intellectual disability panel or overgrowth and macrocephaly panel]) is the most appropriate. Presentation in childhood with macrocephaly and autism/developmental delay is not specific to PHTS, having significant overlap with other syndromic diagnoses. Ongoing follow-up will be of value, to evaluate for emerging symptoms and clinical features suggesting an alternative clinical diagnosis. A Clinical Geneticist should assess the child's syndromic features and review the family history for features typical for PHTS. When there is a family history in adults possibly consistent with PHTS (e.g., characteristic cancers), those family members should be referred for assessment by a Clinical Geneticist and considered for further genetic testing for example, of other genes which have been linked to the Cowden or Cowden-like phenotype (See diagnostic and testing criteria section). A judgment about whether monitoring for PHTS complications is required for the individual and other family members can then be made on the basis of this more complete clinical picture.

8 | MALIGNANCY SURVEILLANCE

PHTS is a cancer susceptibility syndrome and is associated with an increased risk of breast, thyroid, endometrial, renal (mostly papillary), skin, and brain tumors. Several efforts have been made to estimate the risk of these tumors in PHTS (Bubien et al., 2013; Riegert-Johnson et al., 2010; M.-H. Tan et al., 2012). These studies will overestimate the risk through recruitment bias (e.g., by including patients with PHTS diagnosed following a cancer diagnosis). Ultimately, larger longitudinal studies, including patients diagnosed in childhood because of developmental problems, and asymptomatic relatives with PTEN mutations will be needed to more accurately define the risk.

Bubien et al. suggested the cumulative risk for any cancer by age 70 was 85%, with breast (77%) and thyroid (38%) being the most common (Bubien et al., 2013). They also found that this risk of cancer in a female with PHTS was almost twice that of a male, reflecting the predominance of breast cancer. A prospective study by Tan et al. found elevated lifetime risks for breast (85.2%) and thyroid (35.2%) to endometrial (28.2%), colorectal cancer (9%) and melanoma (6%).

There is no international consensus on cancer screening in PHTS. All current guidelines are based on expert opinion. Guidelines have been published by the National Comprehensive Cancer Network® (NCCN®), and in the United Kingdom these have been adapted for use in the National Health Service by the UK Cancer Genetics Group (National Comprehensive Cancer Network® (NCCN®), 2019; UK Cancer Genetics Group, 2017).

9 | ONGOING MEDICAL CARE FOR CHILDREN WITH PHTS

The majority of publications focus on malignancy surveillance yet PHTS is a multisystem disorder with nonmalignant manifestations. In our experience, parents are keen to have a summary of manifestations of their rare condition, to inform personalized follow-up by a

TABLE 2 Summary of clinical findings and management considerations for pediatric PHTS Patients

Clinical findings	Management considerations
Development	
Developmental delay intellectual disability autistic spectrum disorder joint hypermobility hypotonia	Refer for developmental pediatric assessment, physiotherapy and occupational therapy assessment as appropriate based on symptom enquiry and examination
Neurological	
Cortical malformation Hemimegalencephaly[a] Ventricular dilatation White matter abnormalities Lhermitte-Duclos (cerebellar gangliocytoma)[b] Cerebellar signs[b] Symptoms of increased intracranial pressure[a] Pseudopapilloedema[a] Intracranial hypertension[a] Seizures[a]	Annual symptom enquiry and neurological examination Though rare, be alert to unusual seizure patterns (given the possibility of cortical malformation). If concerned, consider referral for EEG, MRI, and specialist opinion Arrange ophthalmology review if symptoms consistent with raised intracranial pressure or visual problems Educate parents about seizure presentations in particular focal seizures and immediate first aid.
Growth	
Macrocephaly >2 S.D. Overweight Precocious puberty[a] Scoliosis (idiopathic and secondary to vascular anomaly or hamartoma)	Annual symptom enquiry and clinical examination Monitor head growth and consider imaging and/or referral to neurosurgery if rapid growth crossing centile lines Healthy eating advice and consider dietician referral if raised body mass index percentile
Skin and oral mucosa	
Pigmentation; glans penis, café-au-lait Pitted and acral keratosis (can resemble verrucous/ common wart) Increased risk of malignant melanoma[b] Acanthosis nigricans is unlikely to represent presence of type II diabetes mellitus	Annual symptom enquiry and clinical examination Prompt referral to dermatology of suspicious lesions Sun safe advice
Vascular and lipomatous anomalies	
Lipoma Arteriovenous malformations PHOST Segmental overgrowth (e.g., limb)	Simple lipoma may not require treatment Educate parents about signs of developing vascular anomalies for example, visible vessels, color change, or swelling. Prompt referral for scan and specialist advice of any new and rapidly growing lesions as can be complex involving muscle, nerve, bone, and other tissues.
Oral cavity and larynx	
High palate Cobblestone appearance and/or papillomas of gums and tongue Tonsillar enlargement History of sleep apnoea or snoring Laryngeal polyp[b]	Gingival lesions may compromise dental hygiene. Regular dental check and consider maxillofacial referral for removal of tongue papillomata. Specific enquiry about snoring/sleep apnoea symptoms/daytime somnolence and recurrent URTI. Consider respiratory studies for sleep apnoea Consider referral to ear, nose, and throat surgeon Caution pre-operatively with regard to anesthetic risk of laryngeal polyp/ airway papillomatosis
Gastrointestinal	
Gastro-intestinal polyps; no risk of malignancy in childhood but polpys may predispose to anemia	Annual symptom enquiry and consider fecal occult blood testing and full blood count Caution parents of features of intussusception. In a presentation with acute abdominal pain, this should be higher up the differential diagnosis list in a child with PHTS.
Thyroid	
Nodule, multinodular goiter, risk of thyroid malignancy Hashimoto's thyroiditis/autoimmune thyroid disease	Annual symptom enquiry and clinical examination Low threshold for thyroid function testing and consider including antibody testing for autoimmune thyroiditis. NCCN guidelines® recommend annual thyroid US from diagnosis, including in childhood (no evidence base for this). Discussion in specialist setting (see thyroid section above)

(Continues)

TABLE 2 (Continued)

Clinical findings	Management considerations
Immunodeficiency and autoimmune disease	Reports of immune dysfunction exist; however, these appear to be rare and are very heterogenous. At present, there is insufficient evidence to suggest specific investigations apart from having a low threshold for investigation should autoimmune or immunodeficiency features emerge.

Abbreviations: PHOST, PTEN hamartoma of soft tissue; URTI, upper respiratory tract infection; NCCN®, National Comprehensive Cancer Network®.
[a]Very limited data (single or very few case reports).
[b]Rare in childhood.

pediatrician and other health professionals and to have information for the nonspecialist in an emergency.

In rare multisystem diseases, such as PHTS, a nuanced approach to symptom enquiry and investigation is required. We provide Table 2, (based on reports of presenting features, which may emerge through childhood) as a guide to support physicians to prioritize their differential diagnoses and management in a manner tailored to current knowledge of PHTS. For example, in a child presenting with persistent diarrhea, or abdominal pain, the possibility of a polyp might be considered higher up the differential diagnosis list than in a child without this underlying diagnosis.

At present, no international consensus exists in the care of patients with PHTS. Going forward concerted international efforts and collaboration are required to establish this for the benefit of patients with PHTS and should take into account different healthcare systems and economics.

Some children will encounter few, if any, medical or developmental issues through childhood, beyond those that brought them to medical attention and a PHTS diagnosis in the first place. Given the paucity of prospective evidence and the risk of over-medicalisation, we do not advocate for a heavy screening regimen. The focus of childhood follow-up should be an annual review with a pediatrician with a detailed examination and symptom enquiry, which will guide the need for further investigations. Few proactive management steps are required above a routine pediatric check-up. These include careful neurological, thyroid, and skin examinations, and parental education regarding sun protection, seizures, and intussusception symptoms.

It is not always possible, or practical, to have day-to-day access to a center with specialist knowledge of a rare condition, and so high-quality information to support the multidisciplinary team around the patient should form part of the specialist advice (Department of Health, 2013).

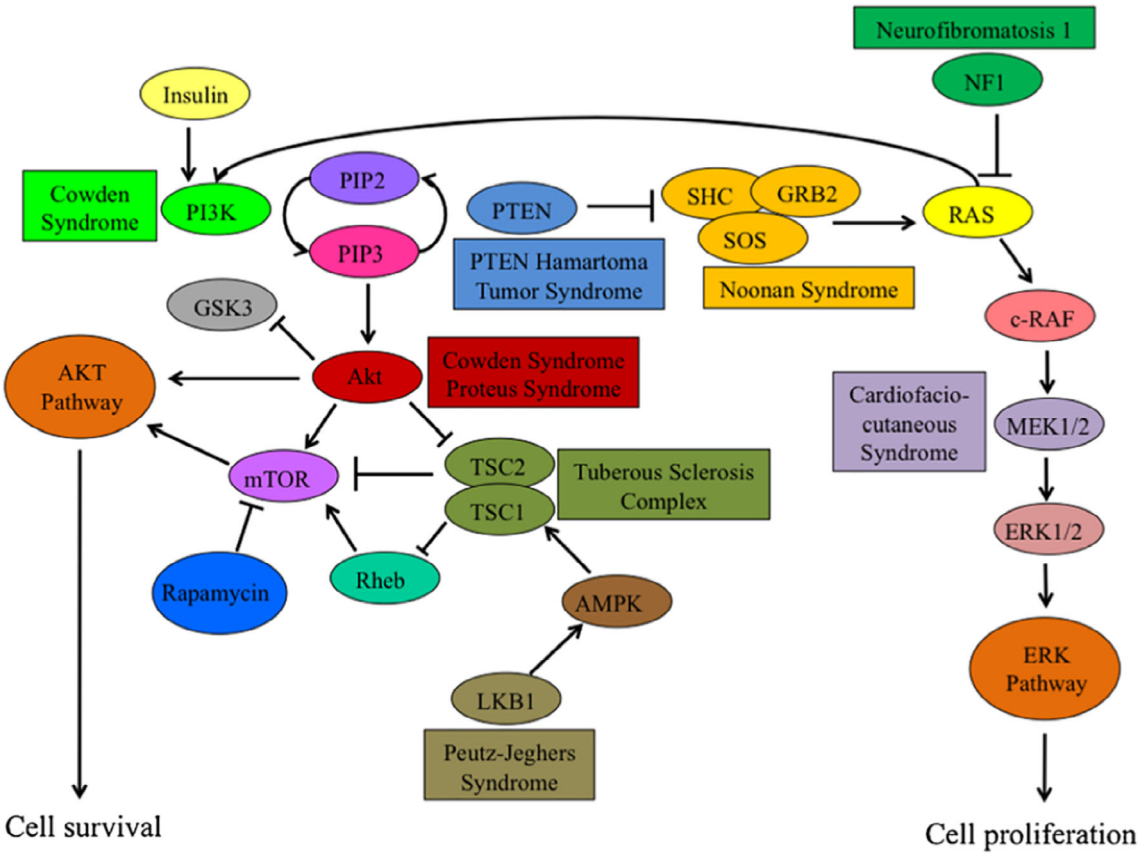

FIGURE 4 PTEN's signaling pathway depicting genes with their corresponding syndromes (J. Mester & Eng, 2013)

10 | CONCLUSION

PHTS comprises a broad range of manifestations from childhood through to adulthood. It is variable and there is age-related penetrance, with new medical issues emerging throughout life. There is no clear genotype–phenotype correlation and so current recommendations for malignancy screening apply to all patients with a likely pathogenic or pathogenic variant, including those diagnosed in childhood as a result of autism, macrocephaly, and other BRRS phenotypes. The originally described phenotypes are useful in quickly describing presentation of a patient or family, and in research, but do not help to differentiate ongoing follow-up.

At present, the pediatric literature mostly consists of small retrospective case series and case reports and hence is likely to have significant selection bias. As more patient registries are established, we are hopeful that better quality prospective data will be accrued, enabling associations to be confirmed or refuted and giving better prognostic information.

Diagnosis of PHTS, predicting likelihood of identifying a PTEN pathogenic variant and discussion around recommendations for cancer surveillance are a strong focus of the clinical literature on PHTS.

We provide strategies for ongoing follow-up of children with PHTS and by review of reports of nonmalignant phenotypes, provide a summary of management considerations with the aim of facilitating earlier recognition and treatment of medical and developmental problems that are commonly and rarely observed in this disorder.

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