Macrocephaly, but neither height nor weight data are useful in the detection of pediatric PTEN hamartoma Tumor Syndrome (PHTS)

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Background

PTEN hamartoma tumor syndrome (PHTS) encompasses different syndromic disorders including Cowden Syndrome (CS), Bannayan Riley Ruvalcaba Syndrome (BRRS), Lhermitte Duclos Syndrome, autism spectrum disorders with macrocephaly and others, which are all associated with germline autosomal-dominant mutations of the tumor suppressor gene *PTEN*. All individuals with PHTS have an increased risk for malignancy and benefit from cancer surveillance strategies. The most frequently affected organs are breast, endometrium and thyroid, but also skin, colorectal, renal and central nervous system tumors have been reported. In the diagnostic workup of PHTS macrocephaly (MC) is an important diagnostic feature. In childhood MC with or without neurodevelopmental disorders is frequently the most evident symptom. To date there is limited data available on prevalence, degree and longitudinal development of head circumference and other auxological data.

Methods

Patient data for height, weight, and head circumferences (HC) were collected from repeated medical exams or prevention check-up visits starting at birth. Growth charts were generated and compared to German reference data. Standard deviation scores (SDS) of HC, height, and body mass index (BMI) were calculated.

Results

We included 23 pediatric patients (8 female, 15 male) with molecular proven *PTEN* gene mutation.

Most male patients demonstrated macrocephaly at birth (73%), whereas only one female patient had documented congenital macrocephaly.

Figure 1 + 2: Head circumference (HC) of male (fig. 1) and female (fig. 2) PHTS patients in comparison to German reference growth charts

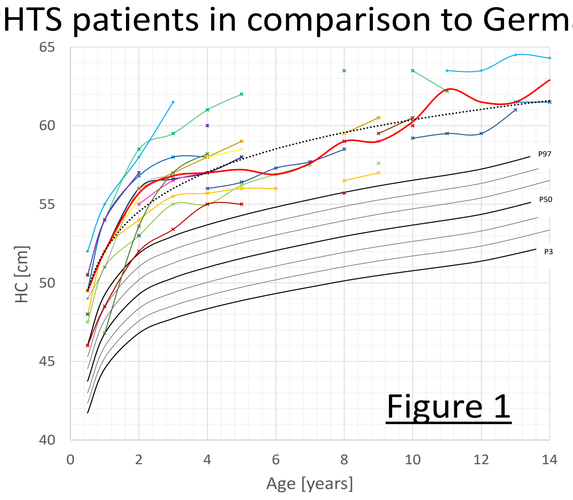

Figure 1

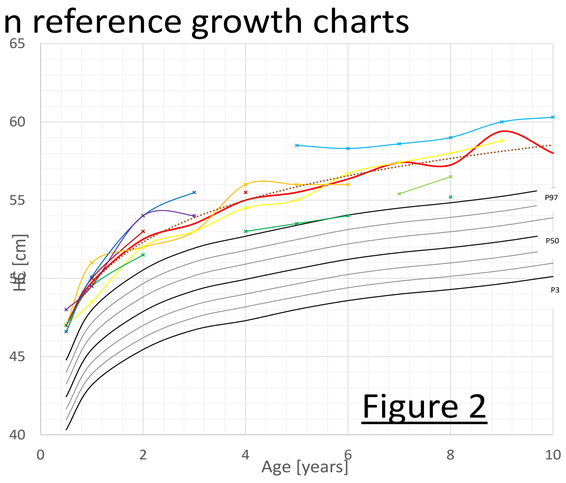

Figure 2

Legend: ____(red): Median, ……Trendline, ___P3-P97. Colored lines: individual patient's HC curves

By the age of two years all patients exhibited a head circumference above the 97th percentile. Stratified for different age groups the median HC-SDSs were between +3.3 and +5.5 in male patients and between +2.9 and +4.1 in female patients. Height, weight and BMI measurements for both sexes were mostly within the normal range. Even though the percentage of overweight and obesity was higher compared to German reference data.

Table 1. Rate of overweight and obesity in pediatric patients with PHTS.

Age in Years	n	Overweight n (%)	Obesity n (%)
0.5	16	4 (25%)	1 (6.25%)
1	17	2 (11.8%)	2 (11.8%)
2	18	10 (55.5%)	3 (16.7%)
3	13	4 (30.8%)	0
4	16	7 (43.8%)	6 (37.5%)
5	17	4 (23.5%)	4 (23.5%)
6	4	1 (25%)	0
7	8	3 (37.5%)	0
8	9	2 (22.2%)	1 (11.1%)
9	8	1 (12.5%)	0
10	5	2 (40%)	0
11	4	0	0
12	4	0	0
13	4	0	0

Figure 3 + 4: Height development of male (fig. 3) and female (fig. 4) PHTS patients in comparison to German reference growth charts

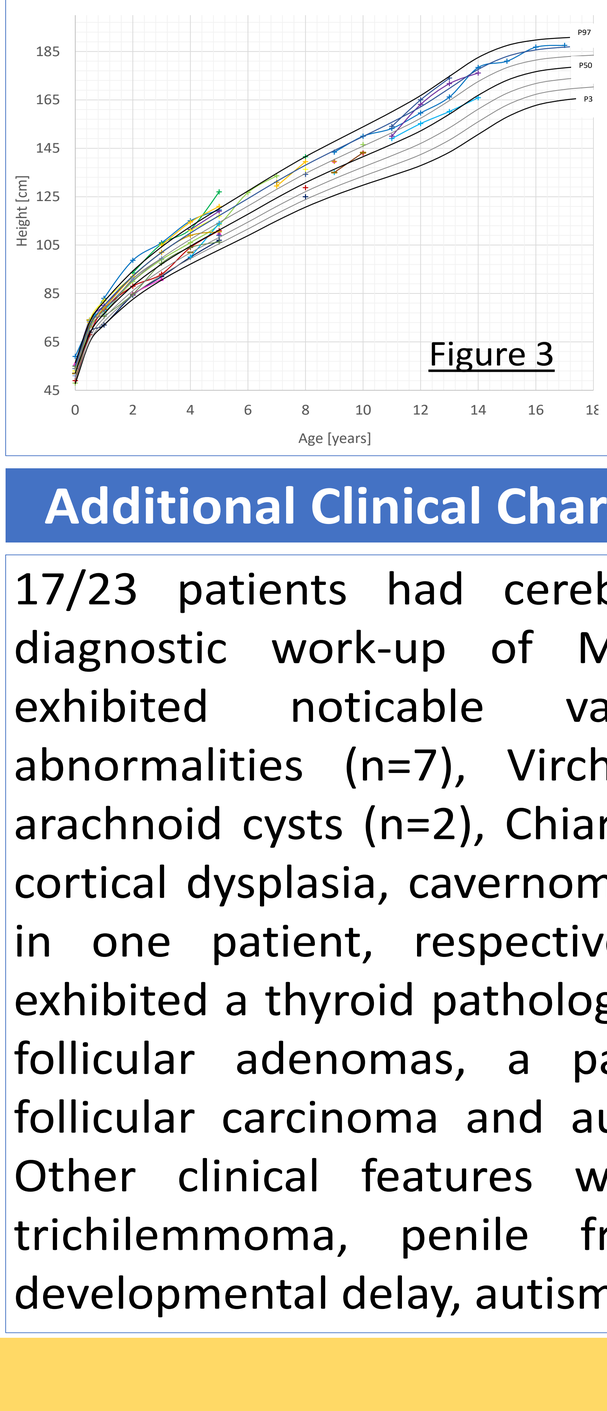

Figure 3

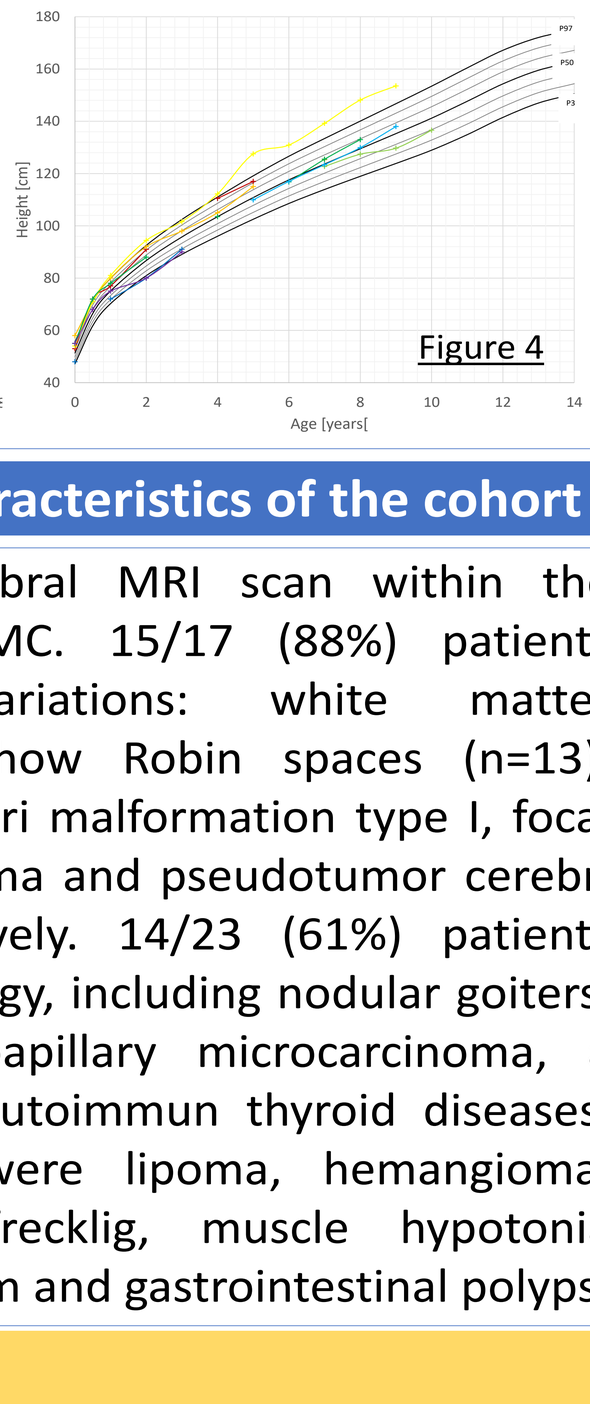

Figure 4

Additional Clinical Characteristics of the cohort

17/23 patients had cerebral MRI scan within the diagnostic work-up of MC. 15/17 (88%) patients exhibited noticable variations: white matter abnormalities (n=7), Virchow Robin spaces (n=13), arachnoid cysts (n=2), Chiari malformation type I, focal cortical dysplasia, cavernoma and pseudotumor cerebri in one patient, respectively. 14/23 (61%) patients exhibited a thyroid pathology, including nodular goiters, follicular adenomas, a papillary microcarcinoma, a follicular carcinoma and autoimmun thyroid diseases. Other clinical features were lipoma, hemangioma, trichilemmoma, penile frecklig, muscle hypotonia developmental delay, autism and gastrointestinal polyps.

Conclusion:

Macrocephaly but no other auxological parameter (length/height, weight, BMI) is helpful in the early identification of PHTS patients. The increase in HC in PHTS patients develops early in life and is more pronounced in males than in females, which might explain the fact that a higher percentage of male PHTS patients are diagnosed during childhood.

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Growth and syndromes (to include Turner syndrome)

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