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Increased head circumference-to-height ratio is an early and common feature in NF1 patients in infancy

Marjo Karvonen [1 2], Marja-Leena Hannila [1], Antti Saari [1 2], Tuula Lonnqvist [3], Leo Dunkel [1 4], Ulla Sankilampi [2]

[1] University of Eastern Finland and [2] Kuopio University Hospital, Department of Paediatrics, Kuopio, Finland, [3] Helsinki University Central Hospital, Department of Paediatric Neurology, Children's Castle Hospital [4] Centre for Endocrinology, William Harvey Research Institute, Queen Mary University of London, London, UK

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Background

Neurofibromatosis type 1 (NF1) is a neurocutaneous-skeletal autosomal dominantly inherited disease caused by mutations in the large *NF1* gene located in chromosome 17 (1). The diagnosis of NF1 is made on individuals who meet two of the seven clinical criteria set by National Institute of Health in 1988 (2). These criteria are sensitive and specific in adult patients with NF1. However, their diagnostic accuracy is not equally good in young children, since their frequency increases by age (3). Children with NF1 tend to be short and macrocephalic (4). Auxological criteria have not been evaluated as diagnostic tools in NF1.

Objective and hypotheses

We hypothesized that a combined auxological indicator, a head circumference-to-height ratio (HCHR), is elevated in NF1 patients at an an early age, and is a useful feature in the diagnostics.

Subjects and methods

Retrospective analyses of growth data and health records of 86 (44 boys, 42 girls) pediatric NF1 patients aged 0-7 years from two university hospital outpatient clinics were performed. Current Finnish growth references of healthy children were used for comparison (5,6). Receiver-operating-characteristic (ROC) analysis was made for HCHR SDS for age at the time of diagnosis.

Then a cumulative prevalence curve for elevated HCHR for age was made by defining the youngest age with HCHR exceeding 1.6 SD or 2.0 SD of each individual.

Table 1. Prevalence of diagnostic criteria (2) and elevated head circumference-to-height ratio (HCHR) for age at the time of diagnosis in 86 NF1 patients aged 0-7 years

Diagnostic criteria of NF1	Prevalence in our data
Cafè au lait macules	96%
Skin fold freckling	23%
Neurofibromas	17%
Lisch nodules	12%
Optic glioma	15%
Osseus lesions	7%
NF1 in 1˚ relative	42%
HCHR ≥ 1.6 SD	66%
HCHR ≥ 2.0 SD	54%

Results

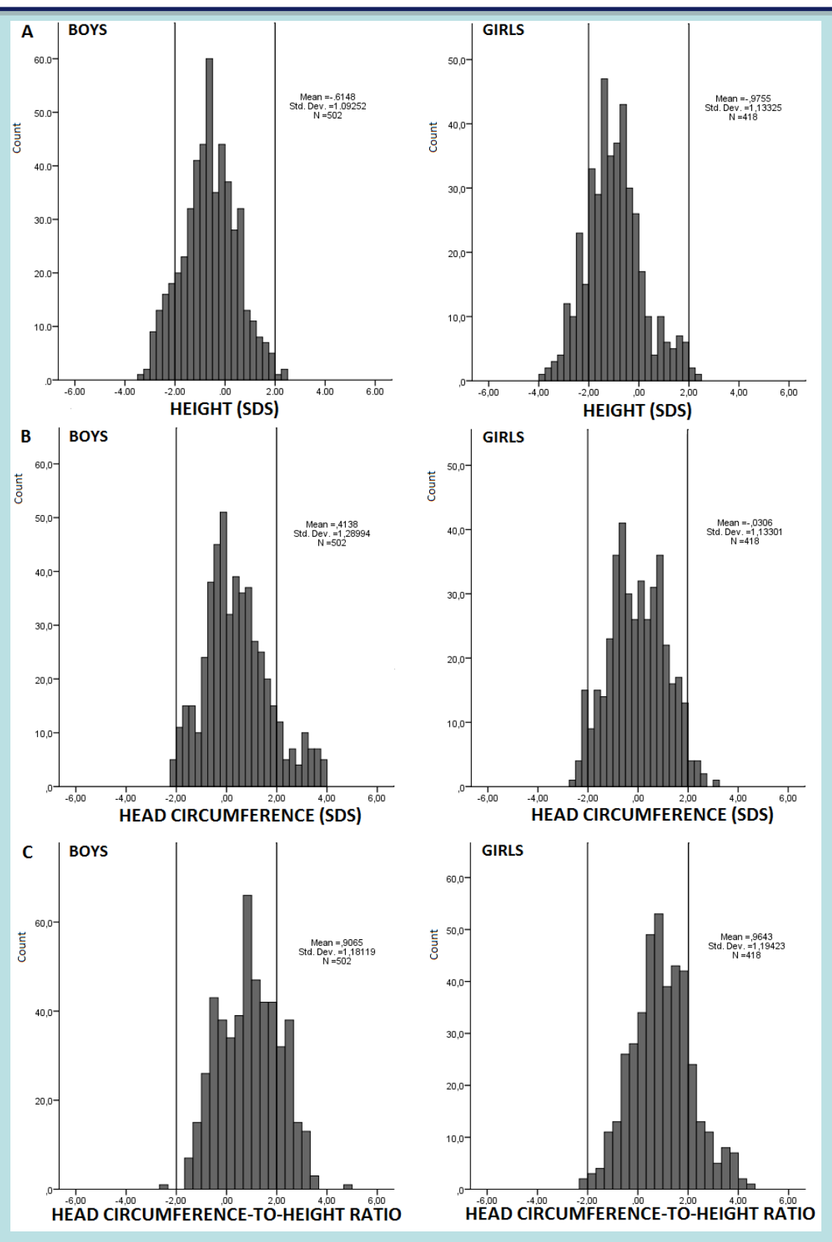

Figure 1. Distributions of A) height, B) head circumference and C) head circumference-to-height ratio (HCHR) measurements in 44 boys (left panel; 502 measurements from 0 to 7.0 years) and 42 girls (right panel; 418 measurements from 0 to 7.0 years) with NF1, in comparison to contemporary population-based growth reference (5, 6).

HCHR was positively skewed and most noticeably outside the +/- 2 SD limits in comparison to height or head circumference alone (Figure 1). The ROC curves for HCHR SD at the time of diagnosis are shown in Figure 2 indicating an optimal cutoff point at 1.6 SD. Cumulative prevalence of the elevated HCHR above 1.6 or 2 SD is shown in Figure 3. At the median age of diagnosis (3.6 y) 66% of children had elevated (≥ 1.60) HCHR. In comparison to existing NF1 criteria, it was the second most prevalent feature (Table 1).

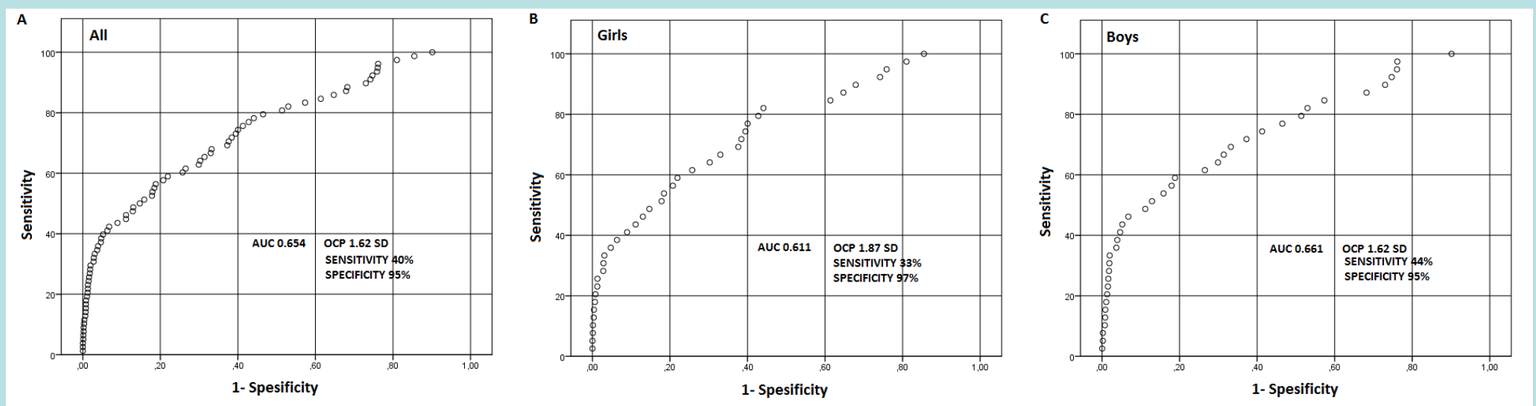

Figure 2. ROC-curves for head circumference-to-height ratio (in SDS) in NF1 children at the time of diagnosis., A) all B) girls C) boys. The OCP (optimal cut off point = sensitivity [2] + spesificity [2]), corresponding sensitivity and specificity, and AUC (area under curve) are shown.

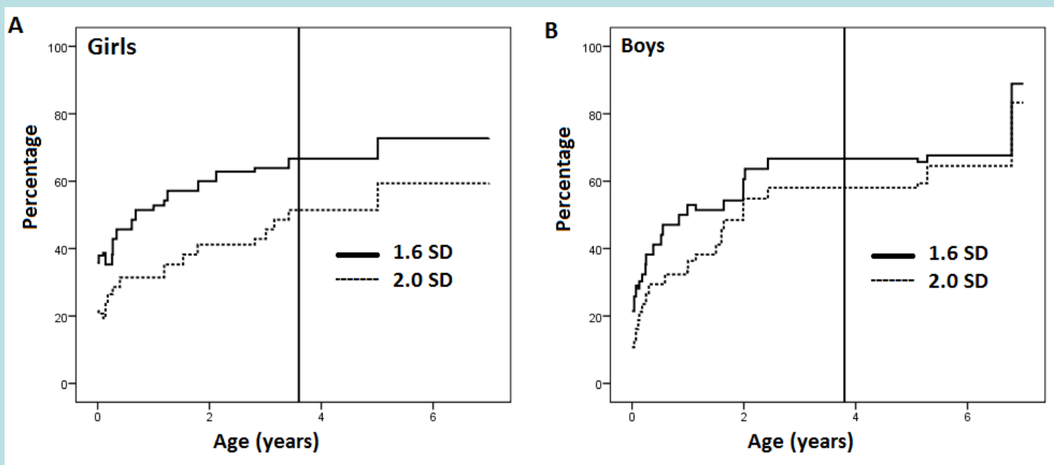

Figure 3. The percentage of children with elevated (higher than 1.6 SD or 2.0 SD) HCHR in A) 42 girls and B) 44 boys. The vertical lines indicate the median age at diagnosis (3.6 y in girls and 3.8 y in boys)

Conclusions

Head circumference-to-height ratio is a simple, easily available and inexpensive auxological indicator, and is elevated in the majority of paediatric NF1 patients at an early age. It is a promising new candidate for a NF1 diagnostic criterion in children.

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