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Noonan syndrome: growth and clinical manifestations in 144 cases

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Abstract. We have analysed growth and the major clinical manifestations of 144 patients (89 males, 55 females) with Noonan syndrome from two West German centres. Size at birth was normal in both sexes. In both males and females, the mean height followed along the 3rd per centile until puberty, but decreased transiently due to an approximately 2 year delay in onset of puberty. Final height approaches the lower limits of normal at the end of the 2nd decade of life. The mean adult height was found to be ($n = 20$) 162.5 cm in males and ($n = 13$) 152.7 cm in females, respectively. Smoothed means and standard deviations for height were derived. These data may be used for the statistical evaluation of height of Noonan syndrome patients. Except for mental retardation and microcephaly, which are more frequent in males, the relative frequencies of minor anomalies and malformations were found to be similar in both sexes. The characteristic non-cyanotic heart defects in the Noonan syndrome do not appear to have a major influence on growth. The auxological data were compared with those in the Ullrich-Turner syndrome.

Key words: Noonan syndrome – Growth – Ullrich-Turner syndrome

Introduction

In 1930 Ullrich [32] and in 1938 Turner [31] described females with a syndrome of short stature, sexual infantilism and a pattern of characteristic minor anomalies including pterygium colli. Later it was shown that the Ullrich-Turner syndrome (UTS) is caused by monosomy X or a structural abnormality of the second X chromosome. Long before the work of Ullrich and Turner, male patients with a similar phenotype had been observed (see Opitz and Pallister [22]). The term "male Turner syndrome" [11] was frequently used when a phenotype resembling UTS was seen in males. On the other hand, in some females with a phenotypic appearance resembling UTS, no chromosome abnormalities could be found. The term "the Turner phenotype" was also used to describe such a phenotypical situation. In 1963 Noonan and Ehmke [18] in reviewing children with congenital heart defects described nine patients – six males and three females – with supravalvar pulmonary stenosis and a distinct clinical appearance. These children were characterized by small stature, hypertelorism, mild mental retardation, and in some instances by ptosis, undescended testes, and skeletal malformations [18]. The term Noonan syndrome is now generally accepted, and the nosologic confusion in the literature has been clarified [16, 22, 23]. In the present paper an attempt will be made to review the characteristics of the syndrome in 144 patients and, in particular, to describe the growth in regard to gender and in comparison with the UTS.

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Abbreviation: UTS = Ullrich-Turner syndrome

Patients and methods

Studies were done on 144 (89 male; 55 female) patients; 62 patients (38 male; 23 female) (Group A) were seen at the University Children's Hospital in Tübingen and 83 patients (51 male; 32 female) (Group B) were seen at the University Children's Hospital in Göttingen. All patients in Group A were seen by two investigators (MBR and/or JRB) and were admitted predominantly for reasons other than suspicion of a congenital heart defect. Patients in Group B were admitted mainly because of a congenital heart defect and were investigated by several physicians. In both centres there was a long standing interest in this syndrome. Thus, in all cases, syndromic and auxological aspects were studied; however, the collection of data was retrospective on the basis of the available documents. In all cases, conventional cytogenetic analysis (cultured peripheral lymphocytes) showed normal chromosomes.

Height (supine length up to an age of 2 years) and weight were measured according to Tanner et al. [30]. Height, weight and bone age data were collected in a mixed longitudinal and cross-sectional mode. When these parameters were measured within a time span of −0.49 and +0.5 years, approximately a full year of chronological age for the purpose of calculating means and standard deviations, the data were attached to the full year closest to the midpoint of the interval. On the basis of these data, smoothed standards of means and standard deviations for each year were derived as described previously [26, 27]. Bone age was determined according to Greulich and Pyle [12]. Birth weights and lengths were compared to the standards of Brandt [4, 5]. Head circumferences (Group A) were compared to the standards of Prader et al. [25]. The syndromic manifestations were based on clinical judgement and assembled in view of the typical abnormal findings reported from other large series [16, 18]. Since it is not the aim of this report to give a detailed account of the relative frequency of all symptoms observed, exact data are given only for some characteristic findings. For descriptive simplicity, abnor-

malities of certain areas of the body were summarized according to Mendez and Opitz [16] unless stated otherwise.

Results

Weight and length at birth

Information on weight at birth was available in 119 cases (Group A: $n = 53$; Group B: $n = 66$). Information on length at birth was available in 95 cases (Group A: $n = 40$; Group B: $n = 51$). Ten children were born before the 38th week of gestation. Four male and seven female patients were small for gestational age. There was no difference between Groups A and B and between the sexes. Weight and length (mean ± SD) of children born between the 38th and 42nd week of gestation were ($n = 55$) 3182 ± 1052 g and ($n = 44$) 51.0 ± 1.9 cm respectively for males, and ($n = 37$) 3219 ± 745 g and ($n = 39$) 51.1 ± 2.4 cm respectively for females. These data do not differ from those of the normal population [4, 5].

Height (length)

All single measurements (392 in the 89 male patients and 355 in the 55 female patients) are depicted in Fig. 1a, b in comparison to the age-related range of normal children [30]. Mean heights related to full years of chronological age of male and female patients of Groups A and B are given in Table 1. Since the data in both groups of each gender were found not to be statistically different, the data from both groups (A und B) were combined and means and standard deviations calculated (Table 1). The mean coefficients of variation of height at each age level were found to be the same in both sexes (4.5% of mean height). Based on these data, smoothed mean heights and standard deviations were constructed. The data are given in Table 2 compared with patients with UTS [26]. Mean cross-sectional height velocities derived from the height data are also given in Table 2 and are illustrated in comparison to normal ranges in Fig. 2a, b. Mean height in males and females follows along the 3rd percentile until about 12 years (males) and 10 years (females). Thereafter height falls below the normal range. A growth spurt indicating puberty (Fig. 2a, b) occurs with a delay of about 2 years and final height is eventually reached at the end of the 2nd decade of life. Height in patients over age 19 years (males, $n = 20$; females, $n = 18$) approaches (mean ± SD) 162.5 ± 5.4 and 152.7 ± 5.7 cm respectively. Since there were insufficient data on parental height available, a correlation between adult height of propositi and mid-parental height could not be calculated. The figures on adult height correspond approximately to the 3rd percentiles of the normal population [30] with females being relatively (the difference is not significant) taller than males. In absolute terms, male patients were found to be taller at all ages.

Weight: height ratio

Weight: height ratios are illustrated in Fig. 3a, b. There was no evidence for a deviation from normality [30].

Bone age

All individual measurements of bone age (males: $n = 119$; females: $n = 78$) in relation to chronological age are illustrated in Fig. 4a, b. Means and standard deviations are given in

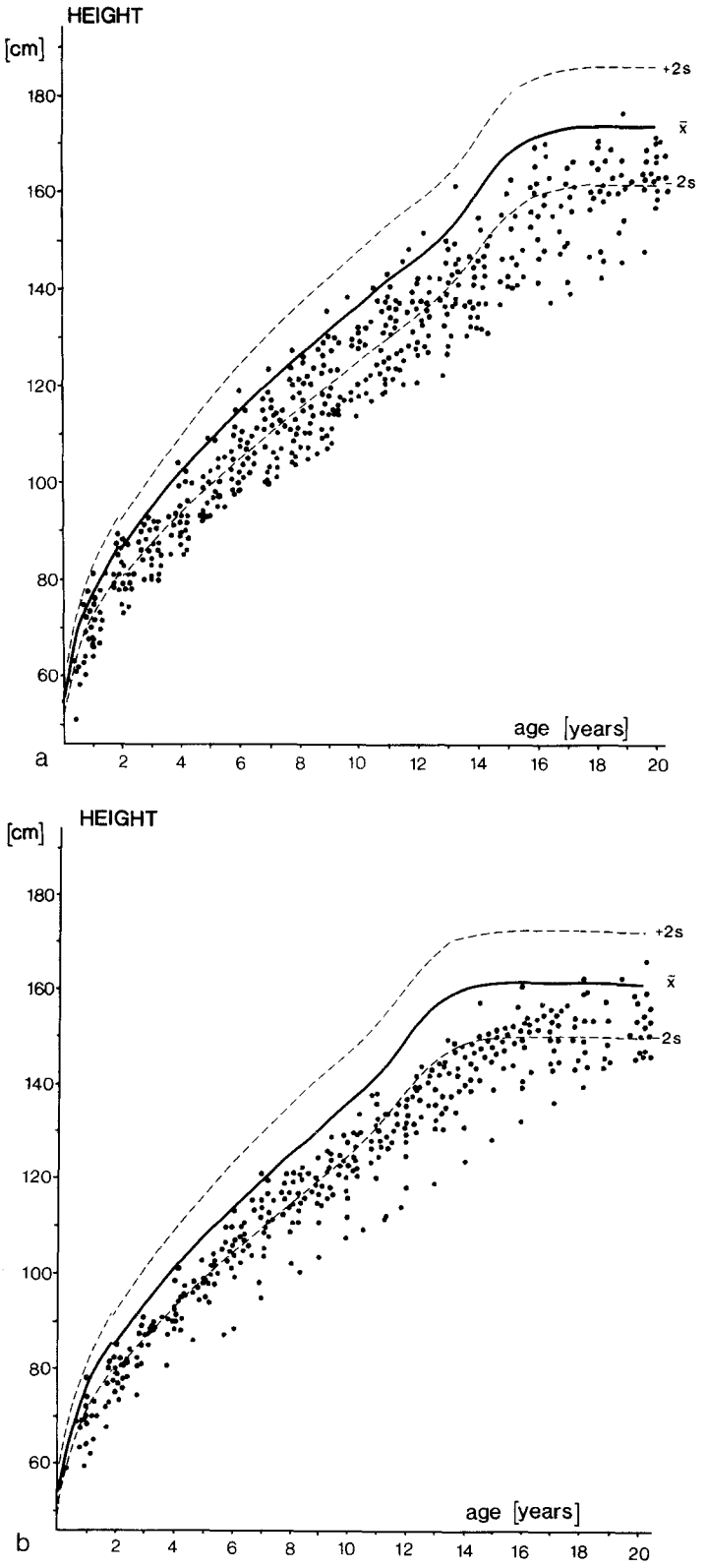

Fig. 1a, b. Height in patients with Noonan syndrome compared to the normal range [30]: **a** males; **b** females

Table 1. In both sexes bone age was, generally, found to be below chronological age at any age. Although there is great scatter, probably due to small numbers, after an age of 5 years bone age tends to be delayed by about 2 years. Compared to the normal population, epiphyseal closure is also delayed by about 2 years.

Table 1. Height (cm) and bone age (years) in patients with Noonan syndrome. N = number of measurements; m = mean; s = standard deviation

Age (years)	Height												Bone age				
	Male patients						Female patients						Age (years)	Male patients Group A + B		Female patients Group A + B	
	Group A		Group B		Group A + B		Group A		Group B		Group A + B						
	N	m	N	m	N	$m \pm s$	N	m	N	m	N	$m \pm s$		N	$m \pm s$	N	$m \pm s$
1	12	70.1	14	73.3	26	71.8 – 3.6	11	67.0	5	71.2	16	68.3 – 4.5	1	3	0.6	1	0.8
2	8	79.0	9	81.3	17	80.2 – 4.4	12	77.0	10	79.5	22	78.1 – 4.0	2	5	1.2 – 0.2	4	1.4 – 0.3
3	8	84.7	14	87.2	22	86.3 – 5.7	13	85.3	4	85.4	17	85.3 – 4.2	3	5	1.7 – 0.6	1	2.5
4	9	89.4	13	95.8	22	93.2 – 4.3	14	91.8	5	95.8	19	95.1 – 4.8	4	6	2.4 – 0.7	2	2.8
5	10	96.6	7	100.9	17	98.4 – 4.8	13	98.9	5	98.1	18	98.7 – 4.4	5	7	3.5 – 1.1	3	3.6
6	11	102.8	14	108.2	25	105.8 – 5.2	12	107.6	8	107.6	20	106.2 – 4.7	6	9	3.9 – 0.6	8	4.1 – 1.0
7	8	106.1	13	112.2	21	109.9 – 5.5	11	109.1	8	113.9	19	111.1 – 6.3	7	3	5.5	4	4.8 – 1.2
8	7	109.7	22	117.7	29	115.8 – 5.4	12	114.9	10	115.1	22	115.0 – 6.0	8	9	5.9 – 1.1	5	5.9 – 1.2
9	10	114.5	17	123.8	27	120.4 – 5.4	11	119.7	8	118.6	19	119.2 – 6.0	9	6	6.6 – 0.5	3	7.3
10	10	123.3	10	128.5	20	125.9 – 6.0	12	124.7	7	122.0	19	123.7 – 6.6	10	7	7.9 – 0.7	4	7.5 – 1.6
11	12	129.7	18	132.1	30	131.1 – 7.3	13	129.6	6	128.3	19	129.2 – 6.7	11	9	8.8 – 1.3	5	8.6 – 2.2
12	8	134.6	17	133.8	25	134.5 – 6.8	13	134.4	9	130.9	22	133.0 – 6.9	12	11	8.8 – 1.2	8	9.9 – 1.8
13	10	136.4	13	140.8	23	138.9 – 8.5	8	140.0	9	136.1	17	137.9 – 7.0	13	7	12.0 – 1.0	6	10.9 – 1.3
14	7	138.3	14	143.8	21	142.0 – 6.6	8	143.7	11	141.6	19	142.5 – 7.1	14	8	10.4 – 1.6	2	11.3
15	6	144.1	8	150.6	14	147.8 – 7.3	5	145.0	11	147.8	16	146.9 – 6.3	15	3	12.0	6	12.5 – 1.2
16	5	148.2	12	155.8	17	153.6 – 8.3	5	147.6	13	150.0	18	149.3 – 6.9	16	7	12.9 – 0.9		
17	6	150.9	6	158.2	12	154.6 – 8.1	4	148.3	11	151.0	16	150.3 – 5.8	17			11	15.0 – 1.1
18	3	154.9	12	162.7	15	161.4 – 9.3	3	148.3	10	151.4	14	150.7 – 6.7	–18	8	14.5 – 1.3		
19	4	157.2	5	160.9	9	159.3 – 6.4	3	150.4	4	151.4	7	151.0 – 7.5	>18	4	16.4 – 0.6	5	15.4 – 1.0
Adult	12	162.5	8	164.3	20	163.2 – 5.4	5	151.4	13	152.7	18	152.3 – 5.7					

Table 2. Height (cm) and height velocity (cm/year) – smoothed values – in Noonan syndrome and Turner syndrome

Age (years)	Height			Height velocity[a]		
	Noonan syndrome		Turner syndrome [27]	Noonan syndrome		Turner syndrome [27]
	Male $m \pm s$	Female $m \pm s$	$m \pm s$	Male m	Female m	m
1	70.8 – 3.2	68.4 – 3.1				
2	80.1 – 3.6	78.1 – 3.5	77.3 – 2.6	9.3	9.6	
3	87.8 – 4.0	86.0 – 3.9	85.1 – 3.5	7.7	7.9	7.8
4	94.3 – 4.2	92.7 – 4.2	91.3 – 3.8	6.5	6.7	6.5
5	100.0 – 4.5	98.6 – 4.4	97.3 – 4.0	5.7	5.9	5.7
6	105.4 – 4.7	104.1 – 4.7	102.5 – 4.2	5.4	5.5	5.3
7	110.1 – 5.0	109.3 – 4.9	107.4 – 4.4	5.1	5.2	4.9
8	115.0 – 5.2	114.3 – 5.1	111.9 – 4.6	4.9	5.0	4.6
9	120.7 – 5.4	119.1 – 5.4	116.2 – 4.8	4.7	4.8	4.3
10	125.3 – 5.6	123.8 – 5.6	120.3 – 5.0	4.6	4.7	4.1
11	130.8 – 5.9	128.4 – 5.8	124.2 – 5.1	4.5	4.6	3.9
12	135.1 – 6.1	133.0 – 6.0	128.0 – 5.3	4.3	4.6	3.8
13	139.2 – 6.3	137.9 – 6.2	131.5 – 5.4	4.1	4.9	3.5
14	143.1 – 6.4	142.9 – 6.4	134.7 – 5.5	3.9	5.0	3.2
15	148.1 – 6.7	146.9 – 6.6	137.6 – 5.7	5.0	4.0	2.9
16	153.5 – 6.9	149.3 – 6.7	140.1 – 5.8	5.4	2.6	2.6
17	157.5 – 7.1	150.3 – 6.8	142.2 – 5.9	4.0	1.0	2.1
18	159.7 – 7.2	150.7 – 6.9	143.9 – 5.9	2.2	0.4	1.7
19	161.4 – 7.3	151.0 – 6.8	145.0 – 6.0	1.1	0.3	0.7

[a] Data of velocity refer to the past year

Head circumference

Head circumferences, available from Group A only, are illustrated in Figures 5a, b in comparison to normal percentiles [25]. All females were normal, whereas in males, 13 out of 23 (57%) were below the 3rd percentile for age.

Minor anomalies and malformations

The relative frequency of some minor anomalies and organic malformations known to be characteristic of the Noonan syndrome in the individual groups (A and B) and in the combined groups of males and females are given in Table 3. The data are compared to the mean relative frequencies reported from larger series of patients with the Noonan syndrome [3, 6, 7, 13, 16, 21, 28] and UTS [14, 15, 28]. With respect to the frequency of certain findings, there were some differences between the two groups of patients (A and B) which were not consistantly related to sex differences. In Group A in both sexes there appeared to be a higher frequency of abnormalities in the area of the thorax, the spine, the skin and the CNS function, while in Group B cardiac abnormalities were more frequent. As expected, pulmonary stenosis was the commonest congenital heart defect in both groups. The relative frequencies of abnormalities found in the combined groups are in good agreement with those reported in the literature. There appeared to be a higher frequency of gonadal abnormalities in males than in females.

Inheritance

In 14 out of 144 patients (10%) a total of 22 first and second degree relatives exhibited all features of the syndrome. In 5 cases the father, in 9 cases the mother, and in 6 cases a brother or sister was affected. In 10 additional cases first-degree relatives with only a few manifestations but not the full picture of the Noonan syndrome were observed. In Group B 23 out of 83 cases had relatives ($n = 30$) with manifestations of Noonan syndrome. The full syndrome was present in 19 (13 families = 16%) cases. In one family the syndrome was observed in 3 generations.

Discussion

In recent years several excellent reviews on the Noonan syndrome have been published [1, 6, 16, 21, 29]. Although this syndrome shares a multitude of findings with the UTS, it is now well established that both syndromes have a different cause [20, 29]. The most obvious difference is that UTS can be proven cytogenetically on the basis of monosomy X or a structural abnormality of one of the X-chromosomes. In the Noonan syndrom, which occurs in both sexes, even using subtle techniques, no structural abnormality of the chromosomes has been found. Moreover, familial occurence is frequent [16, 20]. Mendez and Opitz [16] reported a familial incidence of 22%, a figure somewhat higher than in our populations. Since the phenotype of the Noonan syndrome is subject to developmental changes and there is heterogeneity of manifestations within families, some subtle anormalities may have escaped the attention of the investigators. If familial occurrence cannot be proven in a suspected case, the diagnosis must be established entirely on the basis of clinical criteria. Our patients were seen in two different centres. One group of patients (A) was admitted predominantly for clinical abnormalities including disorders of growth and development. The other group (B) was admitted in order to clarify a suspected cardiac dis-

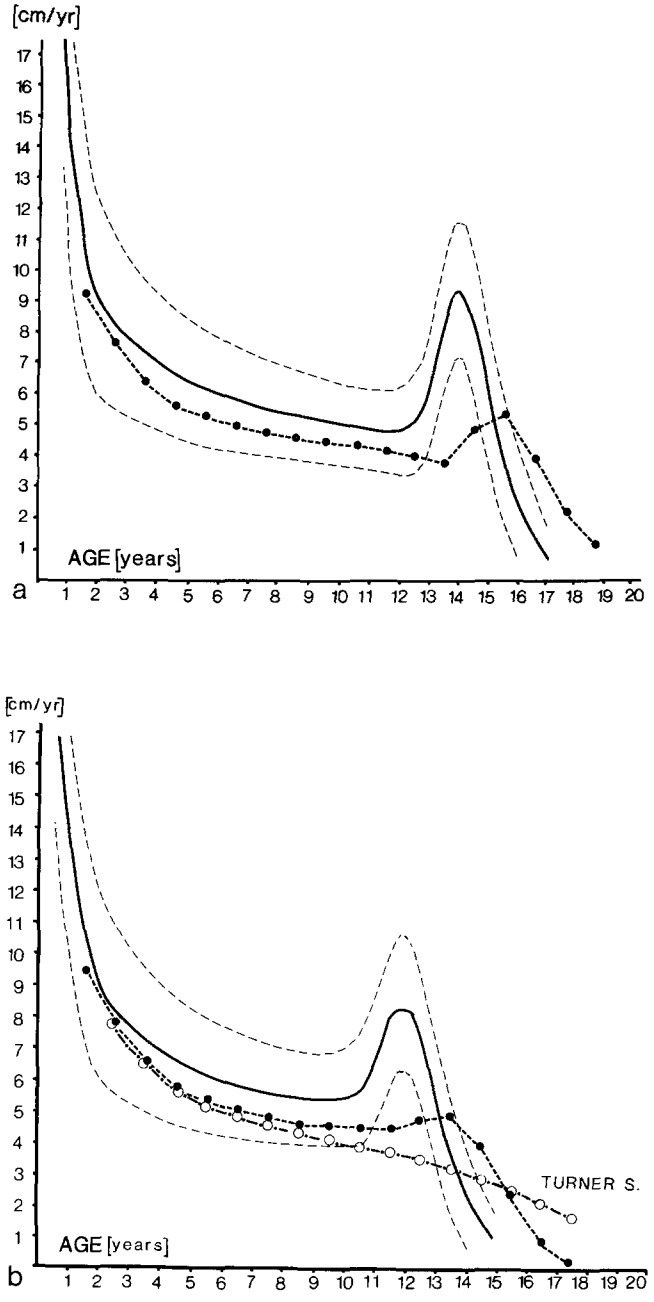

Fig. 2a, b. Mean height velocity in patients with Noonan syndrome compared to the normal range [30]: **a** males; **b** females and patients with Ullrich-Turner syndrome

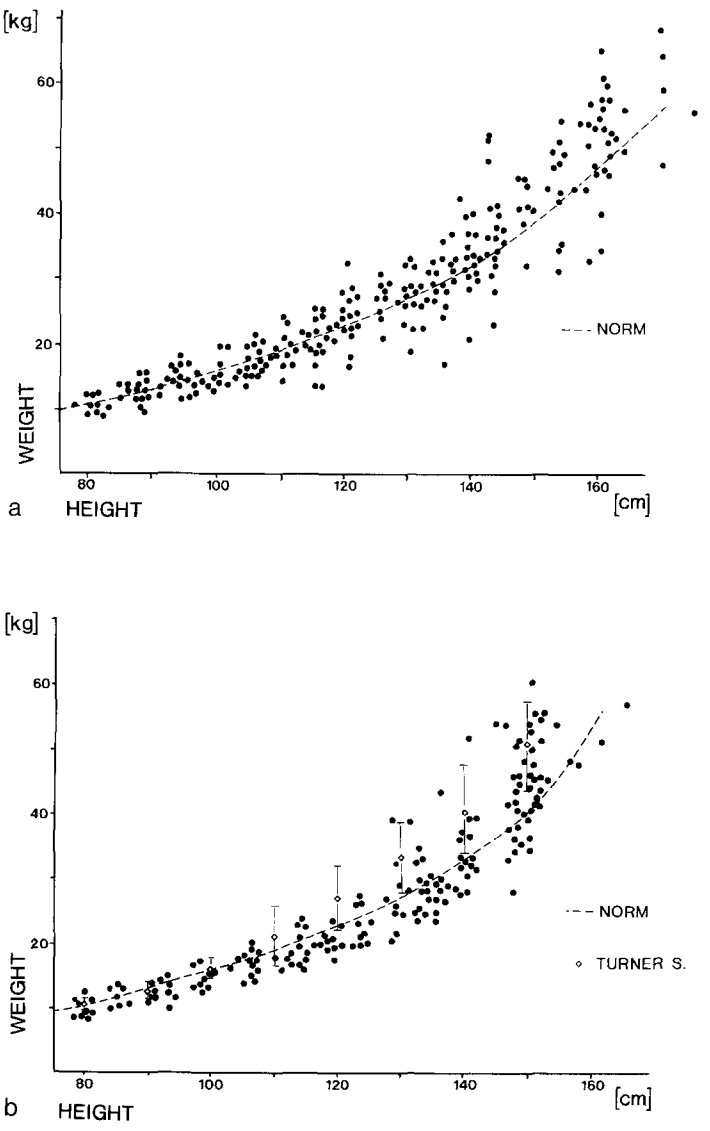

Fig. 3a, b. Weight to height ratio in patients with Noonan syndrome compared to normal means [30]: **a** males; **b** females and patients with Ullrich-Turner syndrome (means ± 1 SD)

order. The technical means to easily verify certain symptoms, particularly by noninvasive imaging of internal organs, have also changed during the period of data collection. All this introduces a subjective element into the collection of the descriptive data and lends some element of uncertainty to the establishment of the diagnosis. In order to circumvent this problem a scoring system has been proposed [8]. However, as the phenotype changes with age [2], the dilemma cannot be resolved completely by such an approach. Nevertheless, it appears to be remarkable that the overall frequencies of abnormal findings seen in our combined groups are in very good agreement with the composite data from several other centres (Table 3). This suggests that the bias introduced by different investigators was compensated for by the number of cases investigated. With few exceptions, most of the manifestations occur with similar frequency in both males and females. In females there was a significantly higher frequency of cubiti valgi. However, this may be due to overestimation by the investigators, since the cubital angle in females is normally greater. Similarly, the higher frequency of abnormalities in the genital region in males may have its cause in its easier access to clinical investigation (e.g. undescended testis). Mental retardation [17] which was observed at a higher frequency in the male population may correlate with a higher incidence of microcephaly. Except for the difference in the frequency of heart defects [24], which is obviously caused by selection, most differences between the two groups appear to be incidental. The differences in the frequencies of minor anomalies between patients with UTS and female patients with the Noonan syndrome seen in our population have also been described by other investigators [16, 18]. Based on pattern of symptoms found in each of the syndromes, a differentiation between UTS and Noonan syndrome can usually be made before conformation by chromosomal analysis.

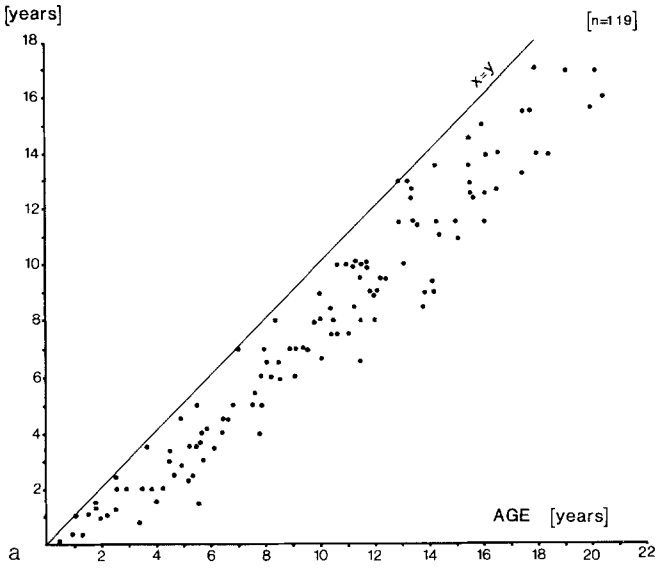

Fig. 4a, b. Bone age (Greulich-Pyle) compared to chronological age in patients with Noonan syndrome: **a** males ($N = 119$); **b** females ($N = 75$)

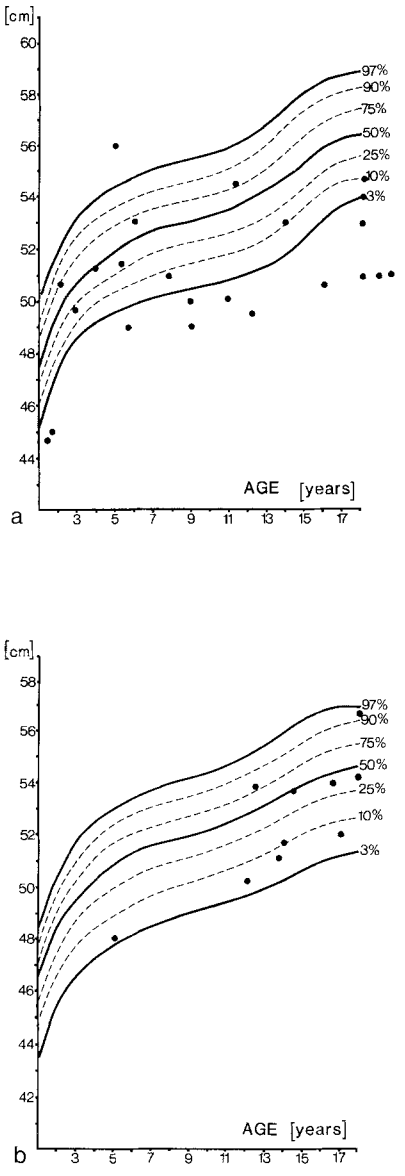

Fig. 5a, b. Head circumference in patients with Noonan syndrome compared to normal percentiles [25]: **a** males ($N = 23$); **b** females ($N = 10$)

In addition, we have investigated the characteristics of the natural patterns of growth. Recently, Witt et al. [33] published the first detailed report on height from birth to adulthood in this syndrome. Since there were more data available to us, a more detailed account of the natural course of growth could be given. This also enabled us to calculate means and standard deviations of height for each year of chronological age, which may serve as "standards" suitable for clinical counselling and a mathematical analysis of data on height in affected individuals (e.g. standard deviation scores). However, in general, the data on height found in our population are very similar to those of Witt et al. [33]. While these investigators attributed some perturbations of growth to heterogeneity, our data show greater homogeneity with a scatter around means close to what is observed in the normal population [30] and in UTS [26, 27]. This contrasts to the heterogeneity suggested by the clinical symptoms and suggests a more uniform cause of the as yet undefined growth disorder [9]. The pattern of growth was found to be almost identical in males and females. This suggests that, if the hypothalamo-pituitary-gonadal axis plays a role in the dynamics of growth, it is similarly effected in both sexes. Since there was no difference in height between Groups A and B, one can assume that the non-cyanotic heart defects, which are frequently present [24], have no major impact on the overall growth pattern. Some of the growth characteristics contrast to the findings in UTS [26]. In the Noonan syndrome prenatal growth is normal, the weight: height ratio stays normal, and there is a delayed pubertal growth spurt. The mean adult height reaches almost the lowest limit of the normal population [30] being approximately one standard deviation higher than in UTS. In both populations, bone age is delayed after birth and progresses in an approximately normal mode during childhood. Similar to the UTS, adult height is not reached until the end of the 2nd decade of life. As in UTS, the

Table 3. Frequency of symptoms (%) in Noonan and Turner syndrome. M = male; F = female; §, & = data summarized from various authors, see text

Abnormal symptoms	Noonan syndrome							Turner syndrome (&)
	Group A		Group B		Group A + B		(§) M, F	
	M	F	M	F	M	F		
Eyes	65	82	69	87	72	85	87	29
Ears	81	72	67	44	73	56	63	58
High arched palate	70	72	43	66	55	69	51	61
Micrognathia	49	47	33	50	40	49	41	67
Neck	74	61	59	63	65	62	78	58
Low-set hairline	60	78	65	53	63	63	61	80
Thorax	70	74	51	28	59	47	64	76
Cubitus valgus	27	55	44	59	38	78	67	50
Limbs[a]	62	67	50	57	55	61	Ca. 50	54
Spine[b]	38	40	26	28	31	33	Ca. 30	15
Skin	50	57	22	35	34	44	32	74
Heart defect (all)	62	63	96	100	81	85	56	20
Pulmonary stenosis	46	29	71	75	60	56	42	Rare
Coarctation	14	29	14	9	14	17	3	14
Renal	8	17	2	3	5	9	25	57
Gonads (male)	81		71		75		72	–
(female)							Rare	95
Mental retardation	62	50	39	31	49	39	44	11
N =	38	23	51	32	89	55	410	387

[a] Short or long fingers, syndactyly, camptodactyly, short hands and feet
[b] Kyphosis, scoliosis, vertebral anomalies

pathogenetic nature of the Noonan syndrome is presently obscure. In the future, new methods in genetics may uncover the molecular basis for the similarities and differences between the two phenotypically similar disorders. This may also provide a rationale for the treatment of those cases with severe growth retardation.

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