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Normal onset of clinical puberty for age in growth hormone-treated children with Noonan syndrome or Turner syndrome: data from the NordiNet® IOS and ANSWER Program®

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Disclosure Statement
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Background

- Noonan syndrome (NS) and Turner syndrome (TS) are separate genetic disorders with similarities in phenotype, including short stature.[1–3]
- Treatment with exogenous growth hormone (GH) is a recommended therapeutic option for short stature associated with TS and NS.[1–4]
  - GH therapy is most effective in promoting linear growth in the childhood years before the onset of puberty and epiphyseal plate closure; therefore age at puberty onset and pattern of puberty progression have important effects on growth pattern and adult height.
- Even though delayed sex hormone treatment in patients with TS is being questioned, common clinical practice is to postpone oestrogen-replacement therapy until the mid-teens because of the widely held view that oestrogen reduces adult height by accelerating epiphyseal fusion.[2,5,6]
- The NordiNet® International Outcome Study (IOS) and the American Norditropin Studies: Web-Enabled Research (ANSWER) Program® are long-term, observational studies designed to collect information on GH therapy in real-world practice.[7]

Aim

- To describe the onset of clinical spontaneous or induced puberty in GH-treated children with NS and TS in the NordiNet® IOS and the ANSWER Program®.

Methods

- The overall study design and protocols of the ongoing NordiNet® IOS and ANSWER Program® are described in detail elsewhere.[7]
- This study population comprised children with NS and TS who were enrolled in either programme and had records on their sexual maturation.
- Onset of puberty was defined as the midpoint between last pre-pubertal record and first pubertal record.
- Physical evidence of puberty, independent of whether endogenous or induced by sex hormone treatment, was defined clinically by Tanner breast stage ≥II (inspection or palpation) or testicular volume ≥4 mL (or Tanner stage ≥GII).
- Due to sample size discrepancies (unbalanced data), statistical comparison on puberty onset between NS and TS patients was not possible. Thus, these results are descriptive and presented as mean ± standard deviation unless stated otherwise.

Results

- The study population included 15 female and 37 male NS patients and 487 TS females with available data recording the onset of puberty (Table 1).

Table 1 Characteristics of children with Noonan syndrome and Turner syndrome with puberty recordings.

Indication	Gender	HSDS at start of GH therapy*	HSDS at puberty onset	Age at start of GH therapy	Age at puberty onset
NS	Male (n=37)	–2.49 ± 1.25 (n=36)	–1.90 ± 1.26 (n=37)	10.34 ± 2.67 (n=37)	12.46 ± 1.51 (n=37)
NS	Female (n=15)	–2.58 ± 0.90 (n=14)	–2.19 ± 0.89 (n=15)	9.21 ± 3.18 (n=15)	11.61 ± 1.38 (n=15)
TS	Female (n=487)	–2.74 ± 0.92 (n=429)	–2.17 ± 1.05 (n=479)	9.72 ± 3.28 (n=487)	12.91 ± 1.87 (n=487)

GH, growth hormone; HSDS, height standard deviation score.
*Since onset of puberty was the main point of the analysis, the availability of the HSDS at the start of GH therapy was not an inclusion criterion.

- The mean age at the start of GH therapy was 10.01 ± 2.84 years in NS and 9.72 ± 3.28 years in TS patients.
- The mean age and distribution of ages at puberty onset in NS and TS patients are shown in Table 1 and Figures 1 and 2.
- At the start of GH therapy, the height standard deviation score (HSDS) was consistent with short stature; mean HSDS was –2.52 ± 1.16 in NS and –2.74 ± 0.92 in TS patients (Table 1).
- Figure 3 presents HSDS in relation to start of GH therapy and puberty onset in NS and TS children.

Figure 1 Age at puberty onset in (A) male and (B) female Noonan syndrome patients (n=37 and 15, respectively).

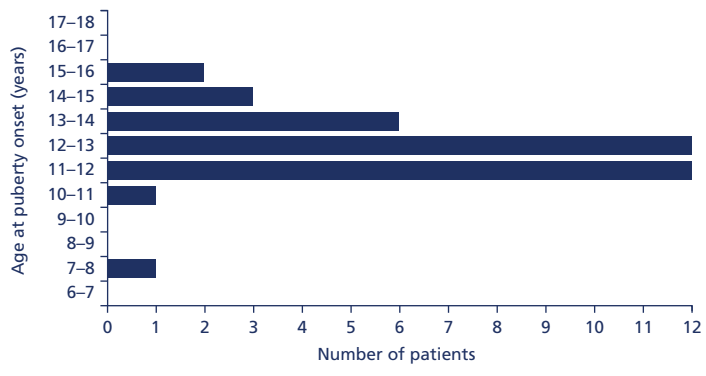


Figure 2 Age at puberty onset in female Turner syndrome patients (n=487).

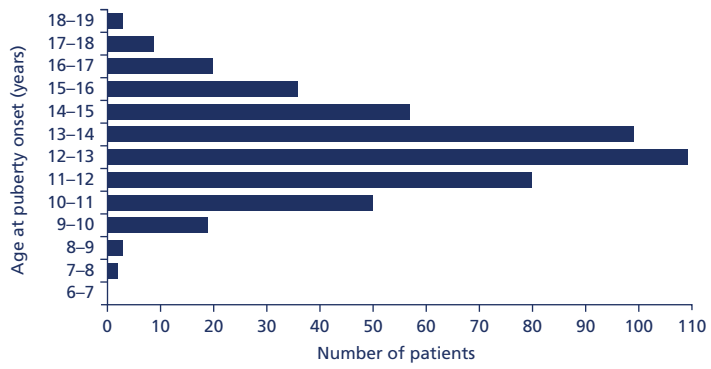
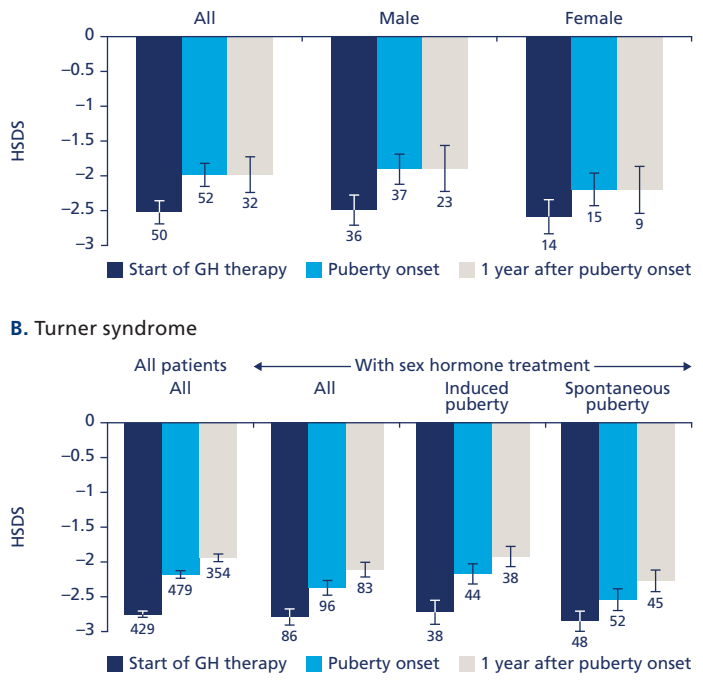


Figure 3 Mean (± standard error) HSDS* in relation to start of GH therapy and puberty onset, and to sex hormone therapy (Turner syndrome patients only).



HSDS, height standard deviation score.
*Since onset of puberty was the main point of the analysis, the availability of the HSDS at the start of GH therapy was not an inclusion criterion. Values below each bar are the number of patients per group.

TS patients and sex hormone therapy

- Initiation of sex hormone therapy (oestrogen-based therapy) was documented in 98 (20%) TS children (Table 2).
- Turner syndrome children without documented initiation of sex hormone therapy (n=389) were 9.70 ± 3.26 and 12.76 ± 1.89 years of age at the start of GH therapy and puberty onset, respectively.

Table 2 Age of children with Turner syndrome in relation to puberty and reported sex hormone initiation.

TS patients	Age at start of GH therapy (years)	Age at start of sex hormone therapy (years)	Age at puberty onset (years)	Time between sex hormone therapy and puberty onset (years)
All (n=98)	9.80 ± 3.37	13.89 ± 1.69	13.51 ± 1.64	–
Induced puberty (n=45)	9.51 ± 3.58	13.44 ± 1.83	13.93 ± 1.69	–0.49 ± 0.48
Spontaneous puberty (n=53)	10.04 ± 3.20	14.27 ± 1.47	13.16 ± 1.52	1.11 ± 1.21

GH, growth hormone.
Sixty-one patients received oestradiol; 21 conjugated oestrogen; 2 ethinyl oestradiol; 2 ethynodiol and oestrogen; 2 norgestimate and oestrogen; 1 desogestrel; 1 ethylestrenol and 8 received other sex hormones. Two patients in the TS group were excluded as they received luteinising hormone releasing hormone analogues (n=1 buserelin; n= 1 leuprorelin acetate).

- Forty-five patients received sex hormones before the reported onset of clinical puberty (0.49 ± 0.48 years before), and 53 after the reported onset of clinical puberty (1.11 ± 1.21 years after) (Table 2).
- Sex hormone treatment was initiated on average 0.84 ± 1.64 years later in the TS group having spontaneous puberty than in the group where sex hormones were given before the reported onset of clinical puberty.
- TS patients starting sex hormones after spontaneous puberty had similar HSDS at the start of GH therapy; however, they tended to have lower HSDS at puberty onset than patients receiving sex hormones before puberty onset (Figure 3B).

Conclusions

- This analysis suggests that age of clinical puberty onset in GH-treated NS and TS patients occurred within the normal population age range.
- In TS patients receiving sex hormone treatment prior to puberty onset, the mean age at sex hormone initiation was 13.44 years.
- This observational study suggests a tendency to postpone sex hormone therapy in TS patients with a lower HSDS.
- The data from the NordiNet® IOS and ANSWER Program® highlight that clinicians may have become more confident about initiating sex hormone treatment earlier and at a more appropriate pubertal age in TS girls receiving GH therapy.

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