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®

Background

- Noonan syndrome (NS) and Turner syndrome (TS) are separate genetic disorders with similarities in phenotype, including short stature.  
- Treatment with exogenous growth hormone (GH) is a recommended therapeutic option for short stature associated with TS and NS.  
  - 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.  
- The NordiNet® International Outcome Study (IOS) and the American NordiNet® Studies: Web-Enabled Research (ANSWER) Program® are long-term, observational studies designed to collect information on GH therapy in real-world practice.

Aims

- 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.  
- This study population comprised children with NS and TS who were involved 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 ≥I (inspection or palpation) or testicular volume ≥4 mL (or Tanner stage ≥II).
- 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.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Gender</th>
<th>HSDD at start of GH therapy*</th>
<th>HSDD at puberty onset</th>
<th>Age at start of GH therapy</th>
<th>Age at puberty onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS Male</td>
<td>125</td>
<td>-2.49 ± 1.26</td>
<td>-1.02 ± 1.66</td>
<td>3.72 ± 3.37</td>
<td>16.67 ± 3.37</td>
</tr>
<tr>
<td>NS Female</td>
<td>15</td>
<td>-2.58 ± 0.90</td>
<td>-1.25 ± 1.47</td>
<td>2.53 ± 5.02</td>
<td>18.15 ± 5.02</td>
</tr>
<tr>
<td>TS Male</td>
<td>105</td>
<td>-2.74 ± 0.83</td>
<td>-1.12 ± 1.87</td>
<td>2.33 ± 5.02</td>
<td>18.27 ± 4.87</td>
</tr>
<tr>
<td>TS Female</td>
<td>1487</td>
<td>-2.74 ± 0.83</td>
<td>-1.12 ± 1.87</td>
<td>2.33 ± 5.02</td>
<td>18.27 ± 4.87</td>
</tr>
</tbody>
</table>

Gh-growth hormone; HSDD, height standard deviation score.

*First onset of puberty was the main entry for the analysis, the availability of the HSDD at the start of GH therapy was not an inclusion criteria.

- The mean age of 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 (HSDD) was consistent with short stature; mean HSDD was -2.52 ± 1.16 in NS and -2.74 ± 0.92 in TS patients (Table 1).
- Figure 3 presents HSDD in relation to start of GH therapy and puberty onset in NS and TS children.

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

<table>
<thead>
<tr>
<th>Age at start of GH therapy (years)</th>
<th>Time between sex hormone therapy and puberty onset (years)</th>
<th>All (n=98)</th>
<th>Induced puberty (n=69)</th>
<th>Spontaneous puberty (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1.04 ± 1.20</td>
<td>0.91 ± 0.71</td>
<td>1.37 ± 0.70</td>
</tr>
</tbody>
</table>

Conclusion

- This study supports 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 HSDD.
- The data from the NordiNet® IOS and ANSWER Program® highlight that clinicians may have become more confident aboutinitiating sex hormone treatment earlier and at a more appropriate pubertal age in TS girls receiving GH therapy.

References