Short stature and its treatment in Turner and Noonan syndromes

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Purpose of review
We review recent developments in the approach to the treatment of short stature in patients with Turner and Noonan syndromes.

Recent findings
Turner syndrome and Noonan syndrome are clinically defined conditions associated with short stature. The Food and Drug Administration (FDA) approved treatment with recombinant human growth hormone (hGH) for patients with Turner syndrome in 1996 and for those with Noonan syndrome in 2007. Studies have shown that early appropriate use of hGH increases adult height in individuals with Turner syndrome. The combination of hGH and low-dose estrogen may also improve growth and adult height as well as possibly provide neurocognitive and behavioral benefits. Noonan syndrome is a genetically heterogeneous condition. In patients with Noonan syndrome phenotype, investigators have identified disease-associated genes (PTPN11, SOS1, RAF1, KRAS, and others). Treatment with hGH has been documented to result in short-term increases in growth velocity as well as modest gains in adult height.

Summary
Our understanding and management of short stature in children with Turner syndrome and Noonan syndrome has greatly advanced over the years. Recent developments with focus on these two common syndromes will be reviewed.

Keywords
estrogen therapy, Noonan syndrome, recombinant human growth hormone therapy, short stature, Turner syndrome

INTRODUCTION

Short stature in childhood is perhaps the most frequent reason for referral to a pediatric endocrinology clinic. There are several clinically defined conditions and syndromes associated with short stature. Two of these nonclassically growth hormone (GH)-deficient disorders are Turner syndrome and Noonan syndrome. Published works have focused on short stature in children with these syndromes, as well as the use of recombinant human growth hormone (hGH) and other treatment modalities, and their effects on growth and adult height. This review will focus on recent developments regarding stature and growth in children with Turner syndrome and Noonan syndrome.

TURNER SYNDROME

Turner syndrome is a common chromosomal disorder in females that is caused by the partial or complete absence of one X chromosome or the presence of a structurally abnormal X chromosome. Abnormalities can include deletions of the short and long arms, duplications (isochromosomes), ring chromosomes, or mosaicisms. It is estimated that Turner syndrome occurs in about 1/1500 to 2500 live female births [1]. The frequency of 45, X-karyotype is about 1–2% in all female conceptions; however, 90% or more of these undergo spontaneous abortion [2].

There is a wide variation of phenotypic features seen in females with Turner syndrome. They range from the severe phenotype characterized by short

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Curr Opin Endocrinol Diabetes Obes 2012, 19:40–46
DOI:10.1097/MED.0b013e32834ed64e

KEY POINTS

- GH therapy remains mainstay of treatment of short stature in non-GH-deficient disorders such as Turner and Noonan syndromes.
- GH therapy can be safely initiated at a younger age in individuals with Turner syndrome; however, exactly how young remains controversial.
- GH treatment combined with early introduction of low-dose estrogen may improve growth, as well as provide improvements in neurocognitive function and behavior in young girls with Turner syndrome.
- Studies with GH therapy in Noonan syndrome have shown that short-term height increase has been comparable to that seen in Turner syndrome. Its effect on adult height, however, remains to be confirmed.

stature, gonadal dysgenesis, and dysmorphic features to women who may only have slight reduction in adult height or premature ovarian failure [3].

SHORT STATURE IN TURNER SYNDROME

The most constant clinical finding in Turner syndrome is short stature. The cause of short stature in individuals with Turner syndrome is multifactorial. It is characterized by intrauterine growth retardation, growth failure during early childhood (as early as 1 year), an absent pubertal growth spurt, and mild skeletal dysplasias [4,5]. Although girls with Turner syndrome are not classically GH-deficient, a disruption in the GH–insulin-like growth factor (IGF) axis has been reported to play a part in the growth failure [6]. Haploinsufficiency of the short stature homeobox-containing gene (SHOX gene located on the distal end at Xp22.3 and Yp11.3 in the pseudoautosomal region) has been implicated in the short stature seen in individuals with Turner syndrome [6,7].

Comparative data on adult height in individuals of different ethnic background show a difference of up to 20 cm between patients with Turner syndrome and the mean for a given unselected population [8▪,9]. Recombinant human GH, anabolic steroids, and estrogen therapy have also been shown to impact growth in individuals with Turner syndrome. There are certain factors that can improve height velocity and adult stature in individuals with Turner syndrome treated with hGH. These include tall parental heights, young age at treatment initiation, longer duration of therapy, daily administration and adequate dosing.

GROWTH HORMONE TREATMENT IN TURNER SYNDROME

The centerpiece of growth-promoting therapy in Turner syndrome is hGH, which was approved by Food and Drug Administration (FDA) for use in girls with Turner syndrome in 1996. In the past, numerous clinical trials [10–12] and observational studies [13–15] have demonstrated improvements in height velocity and adult height in individuals with Turner syndrome treated with hGH. Traditionally, hGH therapy has been initiated in mid-to-late childhood, when the patient is already 2–3 standard deviations (SDs) below the mean in height. Until recently, controlled clinical trials have mainly focused on girls with Turner syndrome of older age (~8–12 years) in which height gains were reported in the range from 0.8 to 2.1 height SD scores (SDS) [12,16–18]. A multicenter Canadian study demonstrated height increases in girls with Turner syndrome (aged 7–13 years) who were randomized to receive hGH treatment (0.3 mg/kg/week and maximum weekly dose of 15 mg) or no treatment. They were able to follow 61 of the hGH-treated girls for a mean of 5.7 years, in whom the average height reached was 7.2 cm taller than the height of those in the control group [11].

Growth failure in Turner syndrome typically begins prenatally and height SDS progressively decline after birth. Publications have demonstrated that treatment with hGH during the first years of childhood in girls with Turner syndrome has led to significant increases in height. A multicenter clinical trial (Toddler Turner Study, August 1999 to August 2003) reported that hGH treatment initiated between 9 months and 4 years of age (mean age 2.0 years) restored height to within the normal range for about 93% of the girls before the age of 6 years [19]. This opportunity to improve adult height had been limited as many patients are not diagnosed until mid-childhood or adolescence. However, in the past decade, improved guidance in diagnosing Turner syndrome has led to girls being diagnosed at an earlier age, thereby allowing earlier treatment.

Other studies have also investigated the efficacy and safety of hGH in young girls with Turner syndrome. For example, Linglart *et al.* [20▪▪] published data (2011) from an open-label, multicenter phase III study in which girls ($n = 61$) aged below 4 years with Turner syndrome received hGH (0.245–0.35 mg/kg/week) for duration of 4 years. The study showed that 80% of the girls were able to attain improved height (1.09 SD higher than the control group of untreated girls) by the mean age of 6.6 years. The general consensus is that hGH can be safely initiated at a younger age than traditionally

started; however, exactly how young remains controversial. Still, recommendations now support the initiation of hGH as early as infancy to maximize adult height. The Turner Syndrome Study Consensus Group [4] suggested starting hGH therapy as soon as growth failure is demonstrated. Table 1 summarizes selected published studies on adult height gains in hGH-treated individuals with Turner syndrome [11,19,20▪▪,21,22].

Treatment with hGH has an overall favorable safety profile in young girls with Turner syndrome. The careful routine monitoring of IGF-1 levels and glucose metabolism during hGH therapy has been recommended [20▪▪]. There is still a need for longer-term data to provide information on hGH treatment effects on safety and adult height in girls with Turner syndrome in whom hGH treatment is started at a very early young age.

ANABOLIC STEROIDS IN TUNER SYNDROME

Anabolic steroids have been used to impact growth in patients with Turner syndrome for about 30 years. In the past two decades, several trials have suggested that the addition to hGH therapy of a weak anabolic steroid, oxandrolone (Ox) that cannot be aromatized, had positive effects on adult height. Recent studies reported from Europe have renewed interest in anabolic steroids treatment. A Dutch publication [23▪] compared patients treated with hGH combined with placebo (Pl) or Ox in low (0.03 mg/kg/day) or conventional (0.06 mg/kg/day) doses in patients with Turner syndrome from age 8 years and estrogen therapy from age 12 years. The trial concluded that compared to hGH + Pl, the combination of hGH + Ox at the lower dose of Ox of 0.03 mg/kg/day demonstrated increased adult height gain (mean ± SD, 9.5 ± 4.7 vs. 7.2 ± 4.0 cm). With the conventional dose of Ox of 0.06 mg/kg/day, the adult height gain was not significantly different from that on hGH + Pl (8.3 ± 4.7 vs. 7.2 ± 4.0 cm). The lower dose also had relatively good safety profile but resulted in slight delay of breast development. The addition of previously studied conventional dose of 0.06 mg/kg/day of Ox did not demonstrate significant increase in adult height gain and caused virilization in a larger proportion of patients.

A study conducted in the UK ($n = 92$) [24▪▪] used doses of Ox of 0.05 mg/kg/day (maximum of 2.5 mg) and showed that Ox increased adult height by 4.6 cm as compared to the placebo group. No adverse effects (e.g. virilization) directly attributable to Ox were reported in this study. Zeger *et al.* [25▪▪] showed that supplementation with Ox (0.06 mg/kg/day) at mean age of 12 ± 1.7 year in hGH-treated girls with Turner syndrome, increased growth velocity and adult height after 4 years of treatment. The changes in height and height SDS from baseline were greater in the hGH + Ox vs. hGH + Pl groups (26.2 ± 6.7 vs. 22.2 ± 5.1 cm). The addition of Ox at different dose regimens to hGH has produced variable responses in adult height gains. It is important to balance Ox's potential adverse effects with the beneficial effects on stature.

ESTROGEN THERAPY IN TURNER SYNDROME

Ovarian failure is the second major problem associated with Turner syndrome. The use of estrogen

Table 1. Growth hormone trials and adult height gain in girls with Turner syndrome

Study	GH-treated patients (*n*)	Mean age of start (years) (mean ± SD)	Height SDS at baseline (mean ± SD)	Initial GH dose (mg/kg/week)	Mean treatment duration (years) (mean ± SD/mean)	Height SDS gain (from baseline to adult height)
Stephure[†] [11] 2005	61	10.3 ± 1.8	−0.2 ± 0.9[a]	0.30[b]	5.7 ± 1.6	1.6 ± 0.6[a]
Davenport *et al.* [19] 2007	45	1.98 ± 1.01	−1.42 ± 1.0	0.35	2.0	1.1 ± 0.6
Linglart *et al.* [20▪▪] 2011	43[c]	2.6 ± 0.6	−2.6 ± 0.6	0.245	4.0	0.98[f]
	18[d]	2.6 ± 1.3	−1.6 ± 0.4	0.35		
Hsu *et al.* [21] 2008	21	11.5 ± 1.8	−3.2 ± 0.8	0.33	4.0 ± 1.5	1.5[e]
Blum *et al.* [22] 2009	158	10.9 ± 3.1	−2.9 ± 0.8	0.31 ± 0.09	5.6 ± 2.3	1.2 ± 0.8

[†]The Canadian Growth Hormone Advisory Committee.
[a]Age-specific Turner.
[b]GH (growth hormone) dose was given 6 days/week. SDS = standard deviation scores.
[c]Standard dose group (0.035 mg/kg/week).
[d]Low-dose group (0.05 mg/kg/week).
[e]Height SDS at start of growth hormone treatment -3.2 ± 0.8 and height SDS at end of study −1.7 ± 0.9.
[f]Height SDS at start of growth hormone treatment −2.33 ± 0.73 and height SDS at end of study −1.35 ± 0.86.

therapy during adolescence to induce pubertal development has also been studied in children with Turner syndrome. Studies have focused on the optimal age of treatment initiation, route, formulation, and dosage of estrogen-replacement therapy. Estrogen deficiency effects in girls with Turner syndrome can be seen from infancy, as they have elevated gonadotropins and delayed skeletal maturation. Quigley *et al.* [26] published data from a multicenter study conducted in the US, which concluded that the administration of estrogen as early as 8 years of age at variable doses (as low as 25 ng/kg/day) provided no added benefit in adult height gain in patients with Turner syndrome. Physicians have delayed given estrogen in Turner syndrome until the age of 14–15 years. The UK Turner Study [24▪▪] demonstrated a positive effect on adult height gain by 3.8 cm with use of oral ethinylestradiol (year 1, 2 μg daily; year 2, 4 μg daily; year 3, 4 months each of 6, 8, and 10 μg daily) at age 14 years rather than at age 12 years. This was in support of previously published associations between delayed pubertal induction and increased adult height. The study further reported that the use of either Ox or late pubertal induction with ethinylestradiol, in contrast to the combination Ox and ethinylestradiol had a beneficial effect on adult height.

Recent publications suggest that the practice of delaying estrogen therapy should be reconsidered. The theory was put to the test in a study (double-blind, placebo-controlled trial) published in the *New England Journal of Medicine* (2011) [27▪▪]. Nearly 150 girls with Turner syndrome were divided into different treatment groups: placebo, GH alone, estrogen alone or GH and estrogen. The dose of hGH was 0.1 mg/kg three times a week. The doses of oral ethinylestradiol (or placebo) were adjusted for chronological age and pubertal status. The ethinylestradiol in specified doses of 25 ng/kg/day were given to girls 5–8 years of age and 50 ng/kg/day for those older than 8 years of age. After the age of 12 years, the patients in all treatment groups received escalating doses (100–800 ng/kg/day) of ethinylestradiol based on age. The study concluded that the effect on adult height was greater in the GH–estrogen group by 2.1 cm (0.32 ± 0.17 SDS) as compared to the GH group alone. This synergy was suggested to possibly be due to a local increase in responsiveness to IGF-1 or the direct effect (at the skeletal plate) of hGH mediated by the ultra-low dose ethinylestradiol. The results also confirmed that low-dose estrogen does not interfere with GH's effects, and suggests that estrogen at low doses can be safely given to girls with Turner syndrome earlier without concerns about stunting growth. It was also suggested that this combination can provide improvements in neurocognitive function, behavior and self-concept, which may have significant impact on quality of life for these patients [27▪▪].

NOONAN SYNDROME

Noonan syndrome is also a common autosomal dominant disorder with an estimated incidence based on clinical criteria of 1/1000 to 2500 live births, with no sex predominance [28]. The clinical features vary with age and include characteristic facial features (down-slanting palpebral fissures, ptosis, hyperteleroism, low-set posteriorly rotated ears, low posterior hairline and webbed neck), specific heart defects (most commonly pulmonary valve stenosis or hypertrophic cardiomyopathy), chest and spinal deformities, short stature, mild mental retardation and learning disabilities.

SHORT STATURE IN NOONAN SYNDROME

About 50–70% of individuals with Noonan syndrome have short stature [29▪]. In contrast to patients with Turner syndrome, in Noonan syndrome, intrauterine growth is normal. In childhood, mean height usually follows the 3rd percentile, after which it usually declines further when delayed puberty and attenuated pubertal growth spurt tend to occur [30]. Reports on GH-secretory dynamics have been variable as some studies reported normal, whereas others have reported abnormal spontaneous GH secretion [31,32]. This inconsistency seems to reflect the heterogeneity of this condition.

From a genetic standpoint, Noonan syndrome was poorly understood until recently. The genes that cause Noonan syndrome encode members of the RAS-MAPK signal transduction pathway. PTPN11 was the first identified Noonan syndrome gene and the most frequently mutated one, accounting for about 30–60% of cases [28,33]. Other genes identified include KRAS (Kirsten retrovirus-associated DNA sequences), RAF1 (v-raf-1 murine leukemia viral oncogene homolog 1), and SOS1 (Son of Sevenless, homolog 1) [33–36]. Genes for rare cases of Noonan syndrome or Noonan syndrome-like disorders include NRAS, SHOC2, and CBL [37▪]. Genetic testing is available to aid in the diagnosis of Noonan syndrome; however, not all patients with Noonan syndrome have an identifiable mutation. Therefore, clinical diagnosis is still essential.

The prevalence of short stature is higher in PTPN11 mutation-positive patients, than in PTPN11-negative patients. Some individuals with Noonan syndrome carry a heterozygous mutation of the nonreceptor-type protein tyrosine phosphatase,

SHP2 (Src homology region 2-domain phosphatase-2), encoded by PTPN11, which has a role in GH receptor signaling. Mild GH resistance by post-receptor signaling defect was a possible factor that contributed to growth failure in patients with PTPN11 mutation [38,39,40▪]. Different data sets on adult height in non-GH-treated patients with Noonan syndrome have been reported. Witt *et al.* [41] published data in 1986 in which mean adult height was 161 cm in males ($n = 9$) and 150.5 cm in females ($n = 19$) with Noonan syndrome. A few years later Ranke *et al.* [42] reported mean adult height of 152.7 cm in females ($n = 13$) and 162.5 cm in males ($n = 20$) with Noonan syndrome. Then 20 years later, data from the UK reported by Shaw *et al.* [43] showed mean adult height as 169.8 cm in males ($n = 18$) and 153.3 cm in females ($n = 25$) with Noonan syndrome. In a review of heights in 73 adults in North America with Noonan syndrome, Noonan *et al.* [44] reported adult heights below the 3rd percentile in 54.5% of females [Centers of Disease Control and Prevention (CDC) standards <151 cm] and 38% of males (CDC standards <163.2 cm).

GROWTH HORMONE TREATMENT IN NOONAN SYNDROME

Over the past two decades, therapeutic trials of hGH have shown to improve height in Noonan syndrome. Table 2 summarizes selected published studies on adult height gains in hGH-treated children with Noonan syndrome [45–48]. Studies seem to conclude that hGH therapy in patients with Noonan syndrome results in short-term increases in growth velocity. Kirk *et al.* [45] reported that hGH therapy used up to 6 years showed increased height velocity and height SDS (mean increment in adult height was 3.1 cm) in Noonan syndrome patients. However, after 3 years of hGH treatment, there was a waning effect and only a small number of patients improved their height prediction by more than 5 cm.

Several studies, despite using small cohorts, have shown a short-term improvement in the height velocity of short children with Noonan syndrome when treated with hGH. Some have shown substantial height gain during prepubertal years which continues through the pubertal period. The height gain was reported to be 0.6–2.0 SDS, which is equivalent to 4–13 cm [49]. However, the published data involved relatively small studies and lacked matched or randomized untreated controls for accurate comparison. Noordam *et al.* [47] published data ($n = 29$) which concluded that hGH improves adult height [mean gains in H-SDS of +1.3 (−0.2 to +2.7)] in Noonan syndrome with and without the PTPN11 mutation. Further prospective studies are required to confirm long-term effects of hGH on height in individuals with Noonan syndrome.

Noonan syndrome is associated with short stature and cardiac defects, which has raised concerns related to the anabolic effects of rhGH and the possible progression of ventricular hypertrophy. Earlier reports have shown no adverse cardiac events related to hGH therapy, which is reassuring [50,51]. However, given that the prevalence of cardiac defects in Noonan syndrome is high, the recommendation is that regular echocardiographic follow-up be obtained during hGH treatment [47,52]. Another concern is the increased risk of cancer in PTPN11 mutation-positive individuals with Noonan syndrome as compared to the general population. Therefore studies suggest close follow-up in these individuals to determine whether hGH increases the risk of neoplasia [37▪,53▪▪,54▪].

Table 2. Growth hormone trials and adult height gain in children with Noonan syndrome

Study	GH-treated patients (*n*)	Mean age of start (years)	Height SDS[a] at baseline (mean)	Initial GH dose (mg/kg/week)	Mean treatment duration (years)	Height SDS gain[b] (from baseline to adult height)
Kirk *et al.* [45] 2001	66	12.1 (8–15)	−3.1 (−4 to −2)	0.245	5.3 (2–8)	0.6 (0.8)[a]
Osio *et al.* [46] 2005	18	8.2 (3–14)	−2.9 (−4 to −2)	0.231/0.042	7.5 (4–12)	1.7 (0.4 to 0.3); 1.7 (0.5 to 3.1)[a]
Noordam *et al.* [47] 2008	29	11.0 (6–18)	−2.8 (−4.1 to −1.8)	0.35	6.4 (3–10.3)	1.3 (−0.6 to 2.4); 1.3 (−0.2 to 2.7)[a]
Raaijmakers *et al.* [48] 2008	24	10.2	−3.3	0.245	7.6 (4–12)	0.97 (0.6)[a]

[a]According to National Standards.
[b]According to Noonan Standards.

CONCLUSION

Short stature and its management in children with Turner or Noonan syndrome can be challenging. Studies with hGH therapy in Noonan syndrome have shown that short-term height increase has been comparable to that seen in Turner syndrome [55]. Efforts are underway to provide optimal, personalized healthcare to individuals with Turner syndrome or Noonan syndrome. These include earlier treatment with GH and introduction of low-dose estrogen at younger age in individuals with Turner syndrome. Still, areas of potential developments include the effect of hGH therapy on body composition, BMI and glucose tolerance in these individuals. Continued developments on the effects of various treatments on height changes in individuals with Turner syndrome or Noonan syndrome are essential for informed clinical decisions and the development of personalized pharmacological management.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

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