Update on Turner and Noonan Syndromes

Elizabeth Chacko, MD[a], Evan Graber, DO[a], Molly O. Regelmann, MD[a], Elizabeth Wallach, MD[a], Gertrude Costin, MD[a,b], Robert Rapaport, MD[a,*]

KEYWORDS

• Turner syndrome • Noonan syndrome • Growth
• Recombinant human growth hormone • Estrogen therapy

KEY POINTS

- Turner and Noonan syndromes have short stature as a common feature. Both conditions present clinicians with a challenging array of genetic, developmental, cardiovascular, and psychosocial issues.
- Recombinant human growth hormone (hGH) has been approved by the Food and Drug Administration for treatment of short stature in both conditions.
- Long-term follow-up in patients with Turner syndrome treated with hGH have clearly indicated a beneficial effect on adult stature. Although it seems that treatment can be safely initiated in early childhood, the exact age of start of treatment remains controversial.
- Although treatment with hGH in children with Noonan syndrome has shown to increase short-term height velocity comparable to that noted in Turner syndrome, its effect on adult height has yet to be proven.
- Both syndromes, although sharing some common clinical features, have specific characteristic screening, treatment, management, and follow-up pathways.

INTRODUCTION

Turner syndrome (TS) and Noonan syndrome (NS) have short stature as a constant feature; however, both conditions can present clinicians with a challenging array of genetic, cardiovascular, developmental, and psychosocial issues. In recent years, important advances have been achieved in each of these areas. This article reviews these two syndromes and provides updates on recent developments in diagnostic evaluation, growth and development, psychological issues, and treatment options

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[a] Division of Pediatric Endocrinology and Diabetes, Mount Sinai School of Medicine, 1 Gustave L. Levy Place Box 1616, New York, NY 10029, USA; [b] Keck Medical School, University Southern California, 1975 Zonal Avenue, Los Angeles, CA 90089, USA
* Corresponding author.
E-mail address: Robert.rapaport@mountsinai.org

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for children with TS and NS. Treatment with recombinant human growth hormone (hGH) for improving adult height was approved by the Food and Drug Administration (FDA) for both conditions. Long-term studies in TS patients have indicated that early appropriate use of hGH increased their adult height.[1,2] The combination of hGH and low-dose estrogen suggested an added benefit on growth and adult height, as well as on potential neurocognitive and behavioral benefits.[3] In patients with NS, treatment with hGH has resulted in short-term increases in growth velocity and modest improvement in adult height; however, their follow-up has been shorter than in those with TS.[4–7] Further prospective studies are needed to confirm the long-term effects of hGH on adult height in patients with NS.

TS

TS results from a partial or complete absence (monosomy) of one X chromosome or the presence of a structurally abnormal X chromosome.[8] Although approximately 50% of affected individuals have 45, X karyotype and 20% to 30% have mosaicism (45, X, and at least one other cell line), the rest have various structural abnormalities (deletions of short and long arm of X chromosome, duplications, ring chromosomes).[9] TS affects 1 per 1500 to 1 per 2500 live female births.[8,10] The disorder causes short stature, skeletal anomalies, complete or partial lack of sexual development, and infertility; as well as cardiac, endocrine, and kidney abnormalities, and a propensity for autoimmune disease.

Prenatal Diagnosis

Sex chromosome abnormalities are increasingly being detected prenatally by chorionic villous sampling or amniocentesis. Sonography is a useful tool in the prenatal diagnosis of TS. The most common sonographic findings include nuchal cystic hygroma, nonimmune hydrops, and increased nuchal translucency.[11] Other ultrasound findings suggestive of TS include coarctation of the aorta, left-sided cardiac defects, renal anomalies, oligohydramnios, polyhydramnios, and intrauterine growth retardation. Diagnosis of TS can also be suspected in abnormal triple or quadruple maternal serum screening (α-fetoprotein, human chorionic gonadotropin, inhibin A, and unconjugated estriol).[12] However, neither ultrasound nor maternal serum screening are 100% diagnostic and confirmation by karyotype (via amniocentesis or chorionic villus sampling) is necessary.[12,13] The occurrence of 45, X karyotype is about 1% to 2% in all female conceptions leading to a 90% or greater fetal loss.[14,15]

Early detection can help identify cardiac malformations such as bicuspid aortic valve that require treatment to prevent complications. Early diagnosis helps prevent or remediate growth failure, hearing problems, and learning difficulties. Although the recurrence risk for TS is not increased, genetic counseling is recommended for families who have had a pregnancy or child with TS. Prenatal counseling should involve the discussion of the variable features of TS, the likelihood of congenital heat disease, kidney abnormalities, short stature, ovarian failure, and their management. It should be emphasized that most individuals with TS have normal intelligence, but may have specific learning disabilities.[12]

Postnatal Diagnosis

Diagnosis of TS requires a peripheral blood karyotype. If there is a strong clinical suspicion despite a normal peripheral blood karyotype, a second tissue (eg, skin) should be examined. Individuals with the 45, X karyotype tend to have a more characteristic phenotype than those who are mosaic with a normal cell line (45, X/46 XX or 45,