Case Report
Neurofibromatosis Type 1 with Overlap Turner Syndrome and Klinefelter Syndrome

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Summary
Turner’s syndrome is a sex chromosome disorder. Klinefelter’s syndrome is one of the most severe genetic diseases. Neurofibromatosis is an autosomal dominant disorder characterized by cafe-au-lait spots and fibromatous tumors of the skin. In this article, we report the overlap of neurofibromatosis-1 with Turner and Klinefelter syndromes. Thus, these disorders might overlap within the same patient. Due to these cases, we suggest that each patient with Turner-like symptoms or Klinefelter’s-like syndrome, be carefully examined for café au lait macules before the initiation of hormone replacement treatment.

Key words: turner syndrome, klinefelter syndrome, Neurofibromatosis type 1.

Introduction
In 1938, Henry Turner reported seven phenotypic females with short stature, sexual infantilism, webbed neck and increased carrying angle [1]. Half of the cases of Turner syndrome have a 45 X chromosomal complement. Clinical manifestations in childhood include webbing of the neck, a low posterior hairline, small mandible, epicanthal folds, widely spaced nipples and cubitus valgus. Short stature is a cardinal finding in all girls with Turner syndrome [2].

Klinefelter syndrome (KS) was first described in 1942 as a syndrome characterized by gynecomastia, small and firm testes, azoospermia and elevated levels of serum follicular stimulating hormone (FSH) [3]. It is the most common chromosomal aneuploidy occurring in ~0.1–0.2% of the male population. There is at least one extra X chromosome present in addition to the normal male karyotype [4].

Neurofibromatosis (NF) is a common autosomal dominant disorder. There are two distinct forms of NF. NF type-1 (NF-1) is the more prevalent type and is diagnosed when any two of the following signs are present including, café-au-lait macules, axillary or inguinal freckling, Lisch nodules, neurofibromas, a distinctive osseous lesion, optic gliomas and a first-degree relative with NF-1 whose diagnosis was based on the aforementioned criteria. Children with NF-1 are susceptible to neurological complications [5].

NF-1 demonstrates phenotypic overlap in some patients with Noonan syndrome (NS), ultimately resulting in the so-called NF–NS [6]. In addition, NF-1 shows phenotypic overlap with Watson syndrome (WS) [7]. This syndrome is characterized by the presence of pulmonary valvular stenosis, cafe-au-lait spots and low or dull intelligence [8]. Schorry et al. [9] reported two cases, which had both Ullrich–Turner syndrome and NF-1. However, there was no reported association with KS.

In this article, we report NF-1 plus a girl with Turner syndrome on chromosome analysis 45 X and a boy with KS on chromosome 47 XXY.

Case 1
The patient initially presented to us at the age of 15 years, and had the chief complaints about short stature and delayed puberty at 10/12 years of age. Childhood history was unremarkable except for short stature. At her family history, her mother and grandmother had multiple cafe-au-lait macules, axillary or
On her physical examination, at that time, her height was 138 cm (<3p, SDS: –3.57), her weight was 36 kg (<3p, Standard Deviation Score (SDS): –2.94) and her bone age corresponded to that of a 14-year-old girl. Her initial blood pressure was 130/100 mmHg which remained normal on subsequent examinations. She had a round face with micrognathia and her neck was short with the presence of webs. A number of café-au-lait macules and axillary freckling were observed in her body. Her breasts were small, undeveloped and were assessed to be at Tanner stage 2. There was minimal pubic hair. She had webbing of the neck, a low posterior hairline, small mandible, prominent ears, high arched palate and a broad chest presenting the illusion of widely spaced nipples and cubitus valgus. Her spine showed a right thoracic curve. The rest of the clinical examinations were normal (Fig. 1). Her hormonal assays, including FSH (106 IU/l), Luteinising Hormone (LH) (27.3 IU/l), estradiol (11.07 pg/ml), were abnormal. Plasma androgens, thyroid hormone levels and cortisol levels were within the normal ranges. Ultrasonography of the patient’s pelvis showed a hypoplastic uterus, whereas the ovaries were not visible. The karyotype analysis was 45 X. Her eyes showed Lisch nodules during ophthalmologic examinations. The magnetic resonance showed that there was a 5-mm hyperintens nodular lesion in the right posterolateral area of mesencephalon (Fig. 2).

**Case 2**

The patient was a 15-year-old boy who suffered from hyperpigmentation on various parts of his body. He had no family history or stigmata of NF-1.
On physical examination, his height was found to be 165.5 cm (25–50 p) and weight was 45.5 kg (10–25 p). He had gynecomastia, a number of café-au-lait macules and axillary freckling (Fig. 3). His pubic hair in female distribution. His penis was normal and both testicles volume were ~2 ml. The rest of the clinical examinations were normal. In ophthalmologic examinations, there were Lisch nodules in his eyes. His hormonal assays including FSH (77.06 IU/l), LH (26.65 IU/l), total testosterone (240 ng/dl), estradiol (30.67 pg/ml) and the other hormone levels were within normal ranges. Magnetic resonance imaging showed normal results. Karyotype analysis of the patient was 47 XXY.

**Discussion**

Turner’s syndrome is a sex chromosome disorder occurring in one out of 2500 female births and in approximately 50 in 100,000 adult females; it is characterized by retarded growth, gonadal dysgenesis and infertility [1].

Pediatricians are most familiar with the clinical findings that prompt the diagnosis of Turner syndrome in children, namely short stature and other features, such as lymphedema, webbed neck, low posterior hairline and cubitus valgus. A wide range of clinical abnormalities, including cardiac and renal anomalies, may also be found [10–12].

In ~80% of girls with 45,X, Turner syndrome, the single remaining X chromosome is inherited from the mother, and in 20% of these girls, it is inherited from the father [13]. Girls with Turner syndrome also have an increased risk of scoliosis, kyphosis and lordosis [14]. Our patient had thoracic scoliosis.

In 1942, Harry Klinefelter described a small group of males who presented with gynecomastia, small testes, Leydig cell dysfunction and infertility [3]. This association of clinical features was identified as being caused by an extra X chromosome, giving a sex chromosome pattern of XXY. This condition occurs in 1:500 to 1:1000 live births, making it one of the most common of all forms of genetic conditions. Many children with KS present with learning...
difficulties and are frequently labeled as attention deficit disorder [15, 16]. Later in life, individuals with KS are sometimes diagnosed when they request infertility evaluation [17].

NF-1 is caused by mutation in the neurofibromin gene. We could not perform this genetic study. NF is an autosomal dominant disorder characterized particularly by café-au-lait spots and fibromatous tumors of the skin. NF-1 demonstrates phenotypic overlap in some patients with NS, ultimately resulting in the so-called NF–NS. The features of both NS and NF-1 had been first reported by Allanson et al. [18].

It is now thought that Noonan-like features can be part of the phenotypic variations of the NF-1 gene mutation. A few patients with NF-1 and features of NS were subsequently reported [19].

There is a well-known association between NF-1 and NS-like manifestations, but there are a few cases reporting an association between NF and Turner syndrome. In 1996, Schorry et al. reported two girls with NF-1 who were found to have the Ullrich–Turner syndrome. These patients’ first clinical findings were associated with NF, and then chromosomal abnormalities were detected. They presumed that the presence of both disorders in these patients was a chance occurrence of two relatively common genetic disorders. They emphasized that chromosome studies should have been performed in girls with NF-1 who have short stature and Noonan– or Ullrich–Turner-like findings [9].

In this article, we studied a girl who had Turner syndrome’s clinical manifestations and a boy who had KS’s clinical symptom along with the findings of NF. Turner syndrome, KS and NF-1 are all common genetic disorders. Thus these disorders might be overlapping. Due to these cases, we emphasized that each patient with Turner-like symptoms or Klinefelter-like syndrome should be carefully examined for café-au-lait macules. Turner syndrome or KS may be associated with NF-1 and as a result of this, unexpected additional pathologies may be found. Additionally, the dual diagnoses of NF-1 and Ullrich–Turner syndrome or NF-1 and KS include potential risks of hormone therapy such as estrogen or testosterone replacement therapy.

References