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CASE REPORT

Turner Syndrome and Neurofibromatosis 1: Rare Co-Existence with Important Clinical Implications

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Abstract

A 16.5-year-old Indian female presented with secondary amenorrhoea, cubitus valgus, scoliosis and multiple lentigines on the face. Karyotyping revealed mosaic Turner syndrome (TS) with 45, X/46, X iXq. She also had multiple café-au-lait macules and axillary freckles but no neurofibroma and did not fulfil the classic criteria for diagnosis of Neurofibromatosis-1 (NF1). Many of her macules were smaller than 15 mm in diameter, which might be due to her hypoestrogenic state. However, exome-sequencing found a pathologic variant consistent with NF1. She was started on daily oral estrogen, and oral progesterone for 10 days every month with close monitoring for neurofibroma and/or glioma expansion. Co-occurrence of NF1 and TS is extremely rare, TS and NF1 can both affect growth and puberty, cause different cutaneous and skeletal deformities, hypertension, vasculopathy and learning disabilities. Our case highlights the need for genetic testing in some cases with NF1 who do not strictly fulfil the NIH diagnostic criteria. We also emphasize the need for close monitoring during therapy with growth hormone, estrogen and progesterone due to the potential risk of tumour expansion in NF1.

Key words: Turner Syndrome, Neurofibromatosis-1, NF1, Neurofibromatosis-Noonan syndrome

INTRODUCTION

Turner syndrome (TS) and neurofibromatosis 1 (NF1) are two distinct genetic disorders and it is extremely rare for an individual to have both. Nevertheless, the presence of both genetic disorders in a single individual has important clinical implications. Although the genetic mechanisms causing TS and NF1 are not related, both disorders affect growth and puberty, and have cutaneous, skeletal and cardiovascular manifestations. To the best of our knowledge, only five cases of coexistent TS and NF1 are reported in literature as of this writing and almost all of them presented with classic clinical features of both NF1 and TS.[1-4]

In this report, we describe the case of a girl who did not have the classic presenting features of TS or NF1, but genetic tests revealed both these disorders and therefore required close supervision while receiving hormonal replacement. The case highlights important clinical considerations in the diagnosis and management of this dual pathology.

CASE

A 16.5-year-old Indian female presented with secondary amenorrhea for six months. She had spontaneous thelarche at 9 years of age and menarche at 11 years of age, following which she had regular menstrual cycles for five years. She had a history of pulmonary tuberculosis 2 years prior, for which she received antitubercular pharmacotherapy for six months, after which she was declared cured. She was born at term from a non-consanguineous marriage and her perinatal history and her childhood development were unremarkable. At the time of presentation, she was a student of the tenth standard with average scholastic performance. She was lean, had no clinical evidence of hyperandrogenism and had received no treatment before her consultation. There was no history of recent weight loss, chronic stress or malnutrition and she had no history of galactorrhea, headache, seizures or visual deficit.

On examination, her height was 147 cm (between 3rd to 10th percentile; Height SDS: -1.59 SD, Indian Academy of Pediatrics 2015 growth chart references, Upper segment: Lower segment ratio = 0.9:1), her target height being 165 cm; her body weight was 55 kg (between 75th to 97th percentile, Weight SDS = + 0.51), BMI 23.8 kg/m^2 (between 75th to 97th percentile, BMI SDS: +1.06).[5] She had sinus tachycardia with a heart rate of 120/min and had stage 1 hypertension with clinic BP of 136/88 mm Hg. There was mild scoliosis with convexity to the right. She had a grade 1b goitre and grade 2 acanthosis nigricans. She had

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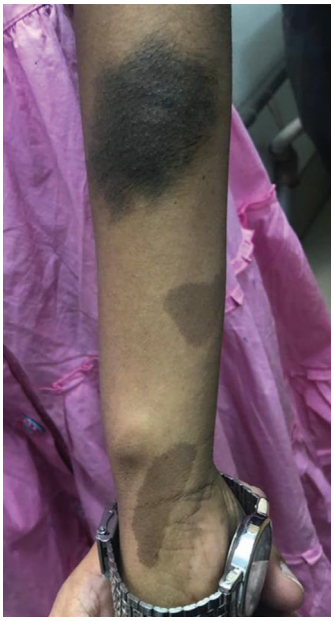

Figure 1. Multiple café-au-lait spots on the forearm.

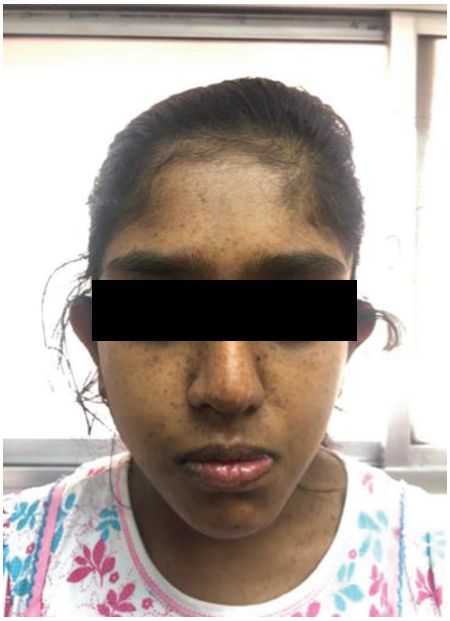

Figure 2. The face of the patient showing multiple lentigines and low set ears.

Figure 3. Cubitus valgus.

multiple café-au-lait macules with dimensions ranging from 5 to 25 mm distributed over her arms, thighs and backs (Figure 1), multiple lentigines over her face (Figure 2) and axillary freckling. She had cubitus valgus (Figure 3) and short fourth metacarpals. Systemic examination including cardiovascular, neurological, respiratory and abdominal examination revealed no abnormalities. Tanner's sexual maturity rating for her was B5P2A0 and she had unambiguous female genitalia with no clitoromegaly or hirsutism.

Initial investigations aimed at evaluating the etiology for short stature revealed normal results for most routinely tested parameters (Table 1). X-ray of her left wrist and hand showed a bone age of 17 years, which corroborated her chronologic age (Greulich and Pyle's atlas). She had subclinical hypothyroidism with TSH 5.6 mIU/ml, normal free T4, and TPO antibody was positive. She had evidence of primary ovarian failure with low estradiol inspite of high FSH and LH.

The clinical findings of proportionate short stature, secondary amenorrhea, cubitus valgus, multiple lentigines over face, scoliosis, hypertension and high FSH levels prompted further evaluation for Turner Syndrome. Karyotype of peripheral blood cells revealed mosaic TS with isochromosome Xq - 45, X [27]/46,X,i(X)(q10)[03] (Figure 4). Following a diagnosis of TS, relevant investigations to screen for comorbidities and complications known to be common in TS were done (Table 1).

The index case had a total of six café-au-lait macules out of which only four had diameters exceeding 15 mm. She also had evidence of axillary freckling. There were no subcutaneous or plexiform neurofibromata and upon slit lamp examination, she had no Lisch's nodules or distinctive osseous lesions like sphenoid dysplasia or tibial pseudoarthrosis. There was no known history of neurofibromatosis in any of her first-degree family members. Thus, she did not fulfil the classic criteria for a diagnosis of NF1, which was chiefly due to the smaller size of her café-au-lait macules than the cut-off of 15 mm required for diagnosis in the post-pubertal age.[6] However, due to strong clinical suspicion, clinical exome sequencing was done which revealed a heterozygous single base pair deletion in exon 21 of the NF1 gene (chr17: g.29556477delA), which was a pathogenic variant consistent with NF1. Home blood pressure monitoring confirmed persistent stage 1 hypertension. Screening for phaeochromocytoma through 24-hour urinary fractionated metanephrines (metanephrines and normetanephrines) was done with normal results. MRI of the brain revealed no optic nerve glioma or CNS tumours.

She was started on estradiol valerate 2 mg daily and medroxyprogesterone 10 mg daily for 10 days every month which induced regular menstrual cycles. She was counselled regarding the poor prospect of future fertility and offered the option for oocyte cryopreservation. During therapy with estrogen and progesterone, she was closely monitored for any new appearance of neurofibromata or worsening of visual acuity or headache for the possibility of optic glioma expansion though she did not develop any of these in her two years of follow-up. She was advised against daily estrogen-progesterone combined pills as a therapeutic strategy to reduce progesterone exposure since there is evidence suggesting the permissive role of progesterone on neurofibroma expansion.

Her bone age was 17 years and X-ray of her knees revealed fusion of her upper tibial and distal femoral epiphyses and therefore she was not initiated on recombinant growth

Table 1. Laboratory investigations and radiology findings

Parameter	Values	Reference range
Hb (g/dl)	12.5	12 – 15.5
WBC count (10^3/ul)	7.3 Neutrophil 52.3 % Lymphocyte 35.6% Eosinophil 3.4% Monocyte 8.1% Basophil 0.6%	4,500 – 15,000
Platelet count (10^3/ul)	287	150 - 450
Urea (mg/dl)	32	17 - 43
Creatinine (mg/dl)	0.66	0.2 – 1.4
FBS (mg/dl)	79	70 – 100
PPBS (mg/dl) 2 hr post 75 g glucose	133	70 - 140
HbA1c%	5.1	
Lipid profile	Total Cholesterol 167 mg/dl LDL cholesterol 104 mg/dl HDL cholesterol 48 mg/dl Triglycerides 138 mg/dl	
LFT	Bilirubin 0.43 mg/dl ALT 31.1 U/L AST 28.8 U/L ALP 135 U/L GGT 22 U/L Albumin 4.04 g/dl Globulin 3.47 g/dl	0.3 – 1.2 3 – 35 3 – 35 33 – 98 5 – 38 3.5 – 5.2 3 – 4.2
Urine R/E	pH: 5 Pus cells: 5 – 6 /hpf No casts/ RBC/ protein/ bacteria	
Serum bicarbonate (mEq/L)	25	22 – 29
Serum Calcium (mg/dl)	9	8.8 – 10.5
Serum Phosphorus (mg/dl)	4	2.5 – 4.5
25(OH)D (ng/ml)	27.8	> 20
USG abdomen and pelvis	Uterus: vol 24.8 cc, endometrial Thickness 3 mm Ovaries: Polycystic in appearance; Left ovary 8.2 cc, Right ovary 8.4 cc Kidneys and urinary tract: Normal	
FSH (mIU/ml)	89.2	1.5 – 11.2
LH (mIU/ml)	22.3	2 – 10
Estradiol (pg/ml)	9.5	27 – 254
Thyroid function tests	TSH (mIU/ml): 5.6 Total T4 (ug/dl): 7.6 Total T3 (ng/dl): 0.99 Anti-Thyroid peroxidase Antibody (U/L): 545	0.3 – 4.5 4.5 – 12 60 – 200 < 34
IGF-1 (ng/ml)	342	226 - 903
Anti-tissue trans-glutaminase IgA Ab Total IgA: 2.7 g/l	1.3 U/ml	< 4 U/ml 0.8 – 3.7
Bone Age (Left hand X ray)	17 yrs	
Karyotype (30 cell)	45,X [27]/46,X,i(X)(q10)[03]	
ECG all leads	Normal sinus rhythm, HR 120 / min	
Echocardiography	Normal cardiac chambers and valves, LVEF 67%	
Cardiac MRI	Aortic size index 1.7 cm/m^2 No abnormality detected in cardiac chambers, valves, ascending or descending aorta	
Pure tone Audiometry	Normal hearing thresholds in both ears	
DXA (Lunar Prodigy) scan for BMD	Z score at AP spine (L1 – L4): -2.3 Left femur neck: - 2.1. Left forearm: -2.4	
IQ test (Weschler's adult intelligence scale)	Verbal IQ scaled score: 95 Performance IQ scaled score: 78	

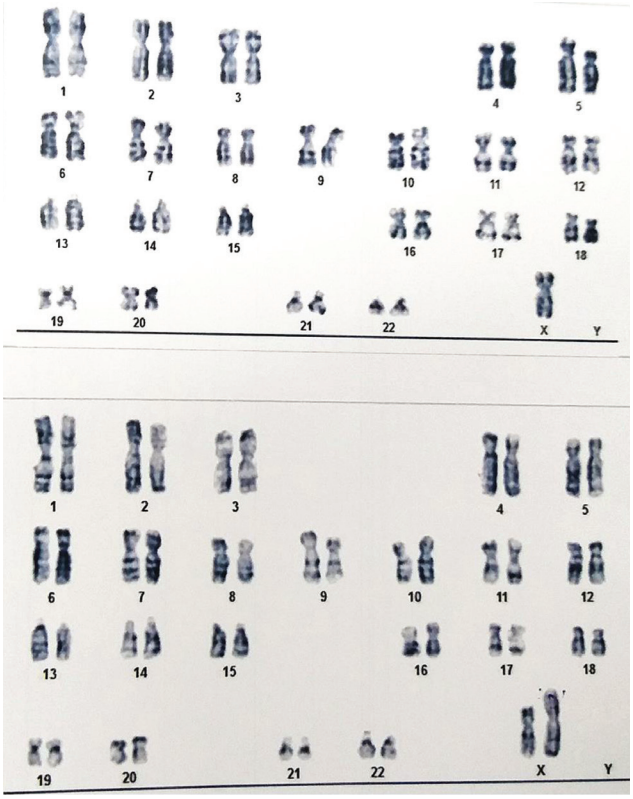

Figure 4. Karyotype 45,X[27]/46, X,i(X)(q10)[03].

hormone therapy. She was given calcium 500 mg/day and cholecalciferol 2000 IU/day for bone health. She was started on metoprolol 25 mg once daily for her hypertension and sinus tachycardia to achieve a target heart rate of 60/min and SBP less than 130 mm Hg. She was periodically monitored with echocardiography and cardiac MRI for aortic root diameter and aortic size index, annual testing of liver function and metabolic profile, pure tone audiometry and BMD-DXA.

Written informed consent was obtained from the patient and her parents for publication of this case report and images of the patient and her genetic tests.

DISCUSSION

The coexistence of NF1 and TS is extremely rare. Due to phenotypic similarities between the two syndromes like café-au-lait macules, many of the published cases presented as diagnostic dilemmas.[2-4] However, in all these cases, the diagnosis of NF1 could be made using the NIH diagnostic criteria.

Our case presented with secondary amenorrhea, short stature, cubitus valgus, scoliosis and short fourth metacarpals, along with multiple lentigines over the face. Although she had some café-au-lait macules and evidence of axillary freckling she did not fulfil the classic criteria required for a diagnosis of NF1, many of her café-au-lait macules were small and did not meet the size criteria of 15 mm required for a diagnosis of NF1 post-pubertally.

It is possible that the hypoestrogenic state due to premature ovarian failure within a few years of attaining puberty inhibited the growth in the size of her macules. Though NF1 is mostly a clinical diagnosis, genetic testing was done for her since there was a high clinical suspicion for NF1, which confirmed a pathogenic variant for NF1

Turner syndrome is one of the most common aneuploidies, seen in one in every 2,500 live births.[7,8] Neurofibromatosis is an autosomal dominant neurocutaneous disorder and the more common variety is NF1 with a prevalence of 1 in 3,000-4,000.[9,10] The diagnosis of TS is based on peripheral blood karyotype showing numerical or structural aberrations of one of the two X chromosomes which can be classic TS (45,X); mosaicism of 45,X with other cell lines and structural abnormalities of X chromosome.[8,11] NF1 is diagnosed based on a set of criteria established by the National Institutes of Health (NIH) which include the presence of multiple café-au-lait spots, Lisch nodules on the iris, optic glioma, axillary freckling, dermal neurofibromas, or distinctive skeletal abnormalities like sphenoid wing dysplasia and/or family history of a first-degree relative with NF1. Two or more must be present in specified numbers to establish the diagnosis.[6] NF1 is caused by pathogenic loss-of-function mutations in the tumour suppressor NF1 gene found on chromosome 17q11.2.[9] Though etiologically unrelated, the presence of the two diseases together can have important clinical implications.

Even though our index case had short height with respect to her target height, she had a height between the 3rd to 10th percentile for healthy Indian girls, and a normal height velocity for age. This, along with the normal progression of breast development and spontaneous menarche in her did not cause much concern to her or her caregivers leading to an overall delayed presentation. Short stature can be a manifestation of both TS and NF 1 but is rarely seen in NF1 alone.[6,7] Short stature in TS is due to several factors including SHOX haploinsufficiency, hypoestrogenism and concomitant disorders like hypothyroidism and celiac disease. Short stature in NF1 may be seen due to growth hormone deficiency or rarely, deficiency of multiple pituitary hormones due to compressive effects of a CNS tumour or following surgery or radiotherapy.[12]

This girl's karyotype revealed the presence of mosaicism of 45, X with 46,X,iX, which explains the spontaneous puberty and the lack of typical Turner phenotype like webbing of the neck or lymphedema.[13] Our case had sparse pubic and axillary hair. Though adrenarche is expected to be normal in TS, however, some studies suggest normal adrenarche but delayed pubarche in TS due to lack of ovarian conversion of DHEAS to active androgen following primary ovarian failure in TS.[14] NF1 is a known risk factor for isosexual precocious puberty in up to 3% of cases with NF1 which is sometimes, but not always, related to the presence of optic nerve gliomas, neurofibromas or other CNS tumours that impinge on neural pathways that inhibit hypothalamic GnRH pulse generator in childhood.[15] Our patient did not have any optic glioma or CNS tumours close to the hypothalamus and had an age-appropriate appearance of pubertal features till she developed premature ovarian insufficiency.

Due to delayed presentation after epiphyseal fusion of long bones, the index case did not receive rhGH therapy. Growth hormone therapy in TS has been postulated to increase the size of melanocytic nevi, though transformation to melanoma is not reported. GHR has been seen to be expressed in plexiform neurofibromas, which are known to be precursors of malignant peripheral nerve sheath tumours.[16,17] The use of rhGH in cases with NF1 is theoretically fraught with the risk of exacerbating the probability for nerve sheath and CNS tumours. However, available data do not support an increased risk of intracranial tumours among NF1 patients receiving GH therapy.[18] Both TS and NF1 are associated with scoliosis, the degree of which might be exacerbated with rhGH. Patients with NF1 and TS receiving rhGH must be closely observed for potential risk of neurofibroma enlargement and worsening of scoliosis.

The effects of estrogen and progesterone treatment on the neurofibromas is another area of concern. It is postulated that subcutaneous and plexiform neurofibromas increase in size and have an increased potential for malignant transformation during puberty and pregnancy, though this has been refuted by some studies.[19-21] Also, females with NF1 possibly have a greater propensity to develop vision loss due to optic glioma than males, as was seen in some reports.[22] This has been attributed to estrogen-mediated activation of microglia and a gender-specific role for cAMP regulation in gliomagenesis.[23-25] Girls with TS are expected to receive lifelong estrogen and progesterone supplements which may lead to a possible increase in the risk for neurofibroma expansion or malignant transformation. Studies have confirmed the presence of progesterone receptors in the majority of neurofibromas and increased proliferation rates of Schwann cells under the influence of progesterone.[26] However, estrogen receptors have been found in very few neurofibromas.[26] Gonadal hormones may lead to neurofibroma development, acting via a noncanonical pathway through GPER-1.[27] Case reports also demonstrate increased tumour growth in girls receiving depot progesterone preparations, but not in those receiving combined oral contraceptive pills.[27,28] Since the effects of progesterone are more established in girls and women with TS and NF1, use of progesterone should preferably be restricted to a maximum of ten days every month rather than a daily combined estrogen plus progesterone pill. Close monitoring is warranted in these women for any increase in the number and size of neurofibroma, any new appearance or worsening of neurologic symptoms and worsening of visual acuity due to progression of optic glioma.

Though hypertension can be seen in TS secondary to coarctation of the aorta, renal failure or as part of metabolic syndrome, the onset of essential hypertension

at a young age is also common.[7,8] Sinus tachycardia due to dysautonomia is also seen in TS, which increases the risk for aortic dissection. On the other hand, hypertension in NF1 needs screening for the presence of pheochromocytoma. Our patient had hypertension with sinus tachycardia. Secondary etiologies were ruled out and she was started on beta-blockers to control her blood pressure and heart rate. TS is known to also increase chances of aortic dissection and is also associated with aortic valve disorders and coarctation of the aorta. Mutations in neurofibromin can also lead to abnormal endothelial and vascular smooth muscle development.[28] The most common vasculopathy in NF1 is renal artery stenosis, followed by coarctation of the abdominal aorta.[29,30] Although the frequency of vascular anomalies in NF1 is low, the concurrent presence of TS and NF1 is expected to significantly enhance the risk for aortic vasculopathy.

Other clinical features common to TS and NF1 are learning disabilities and osseous anomalies in NF1 like bone cysts and dysplasia, which could contribute to craniofacial deformities and hearing defects. Bone cysts or dysplasia can also interfere with the interpretation of bone density by DXA scan which is recommended for osteoporosis screening for all girls with TS. The clinical presentation of NF1 with TS may mimic Neurofibromatosis-Noonan syndrome and Noonan-syndrome-with-multiple-lentigines, previously known as LEOPARD syndrome, due to phenotypic similarities between TS and Noonan syndrome.[31,32] However, karyotype analysis and genetic testing confirmed our index case to have NF1 coexisting with TS.

This was an extremely rare case of the concurrent presence of two distinct genetic disorders -TS and NF1, both of which affect growth, puberty and multiple organ systems. In our case, the café-au-lait macules and neurofibroma did not grow significantly to a considerable size, likely due to the hypoestrogenic state and thus did not classically meet the diagnostic criteria for NF1, which was eventually confirmed through exome sequencing. Genetic testing is indicated for NF1 diagnosis in patients with high clinical suspicion but not fulfilling the NIH criteria. For patients with both NF1 and TS receiving rhGH therapy and gonadal hormones, periodic screening of comorbidities and close monitoring for an increase in the size of macules and growth of neurofibroma and optic glioma is indicated. The use of progesterone should be restricted to a fixed number of days every month rather than daily therapy to minimise the risk of tumour expansion.

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Ethical Consideration
Patient consent was obtained before submission of the manuscript.

Statement of Authorship
The authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
SM: Conceptualization, Methodology, Investigation, Resources, Writing – original draft preparation; **NA:** Validation, Formal Analysis, Investigation, Resources; **SC:** Conceptualization, Validation, Writing – review and editing, Supervision.

Author Disclosure
The authors declared no conflict of interest.

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