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Original Research Paper

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A RARE CASE REPORT OF THYROTOXICOSIS WITH OVERLAPPING DISORDER? NEUROFIBROMATOSIS-NOONAN SYNDROME

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ABSTRACT 14 /Female presented with history of protrusion of eyeballs since last 2 months. She underwent Thyroid Function Test and Ultrasonography Neck in view of swelling on the anterior aspect of the neck. Thyroid profile concluded to be a case of primary Hyperthyroidism (elevated T3 and T4 with TSH<0.005 microIU/L and sonographic finding suggested homogeneous enlargement of thyroid with increased vascularity. Mother also showed concern regarding short stature and non-attainment of menarche. On examination patient had exophthalmos, joffroy's sign and stellwag sign, palmar freckling, webbing of neck, increased carrying angle and short stature. Patient also had tachycardia and hypertension. ultrasonography abdomen-pelvis suggested hypoplastic uterus and ovaries .X- Ray elbow was done to look for ossification and epiphyseal closure. Karyotyping for suspected Turner Syndrome came 46XX. Hormonal workup (Sr. LH, Sr FSH, Sr Cortisol, Sr Estradiol and Sr IGF-1) of which Serum IGF-1came significantly low. Patient was then started on Tab Carbimazole and Tab Propranolol. Gynaecologist advised to induce menstruation through breakthrough bleeding post progesterone pills consumption. Further plan of action is to give Inj Somatotropin in view of short stature. Molecular genetic testing including Hybridization is also being taken under consideration This overlapping Syndromes are not very common to be seen in day-to-day practice and hence should be studied with interest so that early intervention, diagnosis and treatment can be given. Appropriate intervention like Growth Hormone Suppression Test, genomic sequencing and testing and treating Thyrotoxicosis should give a better outcome.

KEYWORDS : Neurofibromatosis-1, Noonan syndrome, Thyrotoxicosis, Growth Hormone deficiency

INTRODUCTION

Thyrotoxicosis refers to the clinical syndrome of excess circulating thyroid hormones irrespective of the source, most common being Grave's Disease followed by Toxic Nodular Goiter.[1] Neurofibromatosis type 1 is an autosomal dominant neurocutaneous multisystem disorder characterized by central nervous system involvement. Other system like endocrine, integumentary and gastrointestinal are also being involved. Noonan syndrome is an autosomal dominant disorder too, its features include short stature, facial dysmorphisms such as a frontal prominence, triangular facies, hypertelorism, downward-slanting palpebral fissures, strabismus, low-set ears, webbed neck, pectus carinatum or excavatum, congenital heart conditions (such as pulmonic stenosis and hypertrophic cardiomyopathy), and cryptorchidism in males. Neurofibromatosis Noonan Syndrome (NFNS) is NF1gene mutation characterized by phenotypic features of both NF1 and Noonan Syndrome. It is a rare RASopathy syndrome (Plexiform Neurofibromas are unusual finding in NFNS).[2] The treatment approach for thyrotoxicosis depends on its underlying cause. Beta-blockers like propranolol are commonly prescribed to alleviate symptoms such as sweating, anxiety, and rapid heart rate. The primary treatment options include thionamide medications, radioiodine therapy, and thyroid surgery.[3] As such there is no specific treatment for NFNS as it is a genetic disorder but early diagnosis and symptomatic treatment can lead to a better outcome.[2] Growth hormone deficiency (GHD) can be observed in patients with NF1 and Noonan syndrome and all the patients with Noonan syndrome or NF1 must be evaluated for Growth Hormone deficiency (GHD).[4]

Case Study

14 years/ female was taken to private practitioner in view of protrusion of eyeballs since last 3 months for which Thyroid profile (T3- 205 ng/dL, T4-16.6 μg/Dl and TSH-<0.005 μIU/ml) was advised which was suggestive of primary hyperthyroidism shown in Table 1. USG Neck was advised and was suggestive of goitrous enlargement of thyroid gland after which the child was referred to pediatric OPD of a tertiary care Hospital for further evaluation and management. Parents also showed concern for short stature and non-attainment of menses. After thorough history and physical examination, it was found that patient also had some noticeable features like café-au-lait spots, low posterior hairline, low set ears, increased carrying angle, axillary and palmar freckling. On anthropometric examination it was found that Height(129cm) and weight(27kg) was <-3SD, suggested pathological short stature as upper segment to lower segment ratio was 0.9:1, Mid parental height was 150 cm and X-ray left hand for bone age estimation came out to be normal. On general examination the child had Tachycardia and Hypertension. Dermatology reference was given in view of café-au-lait spots and freckles, Karyotyping was advised for high suspicion of Turner Syndrome and workup for Neurofibromatosis-1, Watson Syndrome, Noonan Syndrome.

Karyotyping was normal 46XX. Ophthalmologic and fundus examination was done to see for Lisch nodules which was conclusive of nothing. Gynecology opinion in view of non-attainment of menses was taken, physical examination revealed nothing significant and was advised ultrasonography to see uterine and ovarian status. Sonography showed hypoplastic uterus and small ovaries measuring around 2.3cc and 1.8cc. Hormonal study was followed which showed significantly low LH and FSH. Sexual Maturity Rating was conclusive of Tanner Stage I. Patient was then started on Tab Propranolol and Carbimazole. Pediatric Endocrinologist was consulted and was advised Serum Cortisol, Serum IGF-1 and PTH estimation. Serum IGF-1 came out very low (<15 ng/ml), Normal Cortisol and PTH levels. High suspicion of central Hypogonadism by Endocrinologist lead to more set of tests and radiological investigations. Serum Estradiol came low i.e.,37.1 pg/ml. MRI Brain showed small sized pituitary gland with normal signal intensity. Patient was eventually started on supplementation like Vitamin D, calcium and phosphorus

because of significant deficiency. Patient was discharged after running thyroid profile again and was asked to follow up again after 4 weeks.

After 4 weeks T3 and T4 levels came under normal range but TSH was still <0.005 μIU/ml and Anti TPO antibody was found to be elevated. Patient was symptomatically improved and was regularly followed up with proper titration of antithyroid medication.

Summary of all the Investigation is represented through table shown below (Table1)

Table 1

INVESTIGATION	RESULT
TSH|T3|T4 Thyroid Receptor Ab	<0.005 mIU/L↑↑|205.36 ng/dl↑ (73-199) |14.92 μg/dl↑ (4.8-11.5) ↑↑
FSH|LH|PROLACTIN	3.74mIU/ml|1.11MIU↓/ml|335.1μIU/ml
Sr. Cortisol IGF-1 Sr. Estradiol Sr. Testosterone	Normal Very low↓↓↓ Very low↓↓ Normal
Calcium, Phosphate, Vitamin D, Alkaline phosphatase PTH	Decreased↓ Normal
USG (A+P) MRI Brain X-Ray Elbow 2D Echo	Hypoplastic uterus and Ovaries ET=3mm. Right ovary 2.3cc, Left ovary 1.8cc Pituitary gland small in size, Normal signal intensity Corresponds to ~14years of age Normal

PLAN: Patient is planned to undergo Growth Hormone stimulation test after correction of hyperthyroidism. Induction of menses after continuous estrogen and intermittent Progesterone therapy. Injection somatotropin to resolve the problem of GH deficiency and Whole genome exome sequencing to lead to a proper diagnosis for better approach and management.

CONCLUSION

This case highlights the complex interplay of endocrine disorders in a 14-year-old female with multiple presenting symptoms including protrusion of the eyeballs, short stature, delayed menarche, and distinctive dermatological features. The initial findings of primary hyperthyroidism were confirmed with abnormal thyroid profiles, and the goitrous enlargement of the thyroid gland further supported this diagnosis. Additional symptoms such as café-au-lait spots, short stature, and delayed sexual maturity necessitated a comprehensive evaluation.

The diagnostic workup revealed normal karyotyping and ruled out common genetic syndromes such as Turner Syndrome, Neurofibromatosis-1, Watson Syndrome, and Noonan Syndrome. However, the patient's clinical presentation, including hypoplastic uterus and small ovaries, alongside hormonal studies indicating low LH, FSH, and estradiol levels, suggested central hypogonadism. The MRI brain scan showed a small but normal pituitary gland, leading to the initiation of appropriate hormonal therapies and supplementation for deficiencies.

These rare cases require detailed History taking, thorough Examination and are treated on the basis of Investigations supported by clinical Judgement. Regular follow up with cardiologist, Gynecologist and Dermatologist to detect any complications due to prolong hormonal therapy is warranted.

LIMITATIONS

This case has several limitations, including a potential diagnostic delay and a relatively short follow-up period, which may not fully capture long-term treatment effects. The genetic testing was limited to karyotyping, potentially missing other rare genetic conditions, and the endocrine assessment could be more comprehensive to include additional hormone evaluations. Expensive Hormonal workup and genetic testing raise the issue of affordability and accessibility as well. Furthermore, the case lacks detailed functional outcome data and does not address long-term prognosis or the integration of multidisciplinary care. These factors could impact the overall understanding and management of the patient's condition.

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