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Case Report

Fahr's Syndrome; a Rare Presentation of Autoimmune Polyendocrine Syndrome-1 and Carbamazepine-Induced Hypothyroidism

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Abstract:

Autoimmune polyendocrine syndrome type 1 (APS-1) is an autosomal recessive disorder. Basal ganglia calcification, also known as Fahr's disease or Fahr's syndrome, where generalized or partial seizures are one of the common neurological manifestations. However, Fahr's syndrome secondary to APS-1 is extremely rare. This case report describes a 14-year-old girl diagnosed with Fahr's syndrome linked to APS type 1 in the medicine department of Faridpur Medical College Hospital, Bangladesh. The patient presented with recurrent episodes of generalized seizures over the last 4 years, accompanied by weight loss and progressive darkening of skin. Additionally, she had history of absent adrenarche, thelarche, puberchae and menarchae. She has been taking oral carbamazepine over the last 4 years for seizure. Laboratory investigation reveals adrenal insufficiency, hypoparathyroidism, hypogonadism, and secondary hypothyroidism. A contrast-enhanced MRI of brain shows findings suggestive of Fahr's disease. She becomes euthyroid after gradual withdrawal of carbamazepine and initiation of sodium valproate. After administration of glucocorticoid, mineralocorticoid, estradiol, progestin replacement, calcium and Vitamin D supplement her clinical improvement occurred significantly. Eventually her menarchae has started and the patient was referred to Bangladesh Medical University, Dhaka for further management.

Key words: Autoimmune polyendocrine syndrome (APS-1), Fahr's syndrome, Carbamazepine induced central type of hypothyroidism.

Introduction:

Autoimmune poly endocrine syndrome (APS) are mainly 2 types. Among them, APS type 1 develops with endocrine and non-endocrine manifestations in childhood.

The classic triad of APS-1 includes chronic candidiasis of the skin and mucous membranes, adrenal insufficiency, and hypoparathyroidism.

APS-1 is often accompanied by hypogonadism, type 1 diabetes, autoimmune thyroiditis, vitiligo, alopecia, asplenia, pneumonitis, gastritis, pernicious anemia, intestinal dysfunction, nephritis, and hepatitis[1].

Hypoparathyroidism develops earlier than Addison's disease. On the other hand, Fahr's disease is named after Karl Theodor Fahr, a German neurologist who first reported the disorder in 1930[2]. Distinguishing Fahr's syndrome from Fahr's disease is crucial due to

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differences in their etiology, location of lesions, prognosis, and therapy. Currently, Fahr's disease lacks a specific treatment, while Fahr's syndrome requires target intervention based on the underlying cause[3]. Fahr's syndrome can be a cause of epileptic seizures and should be considered in the clinical approach to an epileptic patient, especially in children, teenagers, and young adults[4]. The rarity and variability of APS-I make its recognition challenging. The prevalence of disease components increases over the years and decades, making treatment and follow-up problematic[5]. So, a multidisciplinary approach is always needed.

Case Report:

Our patient, a 14-year-old female, presented with recurrent atonic seizures over the last four years. She had been taking carbamazepine 200mg during this period but her seizures were not fully controlled. Additionally, she complains of fatigue, dizziness mostly during standing from a sitting, and occasional loss of consciousness lasting for 5-10 minutes. These symptoms were more common during fever, diarrhea, or flu-like illness. She also experienced of unintentional weight loss in the last few years, documented by the loosening of clothes and progressive darkening of skin. Menstruation had not been yet begun. There is no history of heat or cold intolerance, skin or dental problems, TB or contact with known TB patient, or prior abdominal surgery. Her parents have a history of consanguineous marriage. Notably, three of her siblings died within a few days after birth without a diagnosis, and her mothers had a history of 2-3 miscarriages. Family history revealed that her brother had epilepsy, hypothyroidism, and chronic mucocutaneous fungal infection. On examination, her axillary and pubic hair absent while labia majora appears normal without any clitoromegaly and vulval swelling. Only the papilla of breasts is developed.

She has a generalized dark skin with hyperpigmented pressure areas and creases. There are multiple black patches on her tongue and oral mucosa. Her recorded blood pressure remained persistently low without any postural drop. Her Serum Cortisol at 9 A.M.: 24 ng/ml. Short Synacthen test result was ACTH at 00 min- 414.60 pg/ml, Serum Cortisol at 00 min- 9.22 µgm/dl, Serum Cortisol at 30 min- 9.64 µgm/dl. Serum electrolytes was Na+: 128.3 mmol/L, K+: 5.07 mmol/L, Ca2+: 7.3 mg/dl, S. Intact PTH: 2.01 pg/ml, S.TSH: 2.82 µIU/ml, FT4: 6.97 pmol/L, S. Testosterone: <0.2ng/ml, S. Estrogen: 26.65 pg/ml, S.FSH: 40.80 mIU/ml, S. LH: 12.28 mIU/ml, RBS: 6.4 moml/L, USG of adrenal gland was normal, USG of pelvic organ showed small uterus for the age & under developed ovarian follicles, contrast, and a non-contrast MRI of brain revealed symmetrical T1 & T2 hyperintensity areas in both dentate nuclei, basal ganglia and both thalami, suggestive of Fahr's disease.

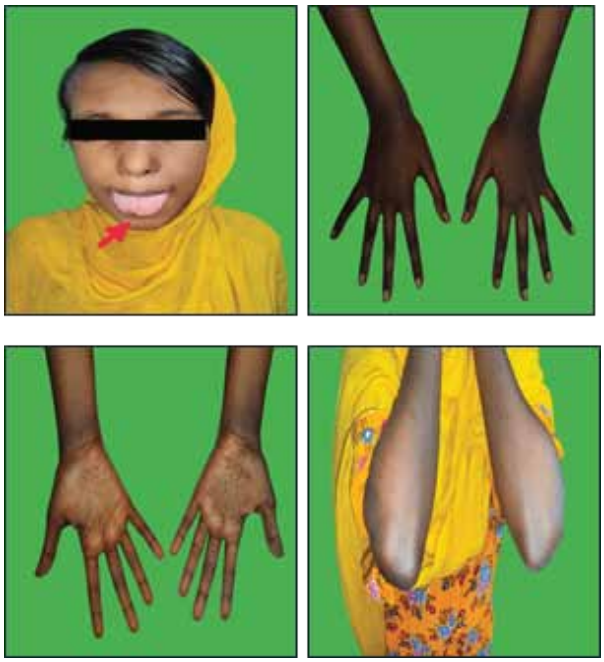

Figure-A: Black patches in tongue.

Figure-B, C, D: Black pigmentation in pressure area & skin creases.

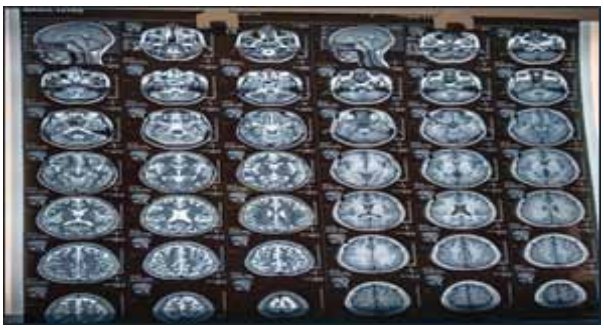

Figure: Contrast and non-contrast MRI of brain: symmetrical T1 & T2 hyperintensity areas in both dentate nuclei, basal ganglia and both thalami, suggestive of Fahr's disease.

The diagnosis was confirmed as Autoimmune polyendocrine syndrome type 1 (components are Addison's disease, Primary hypogonadism, and Primary hypoparathyroidism) with Fahr's disease with secondary hypothyroidism. So, treatment was initiated with oral Hydrocortisone, Fludrocortisone, Calcium, Vitamin D3, Estradiol, Norethisterone, Esomeprazole. Carbamazepine was gradually tapered and replaced by sodium valproate. Additionally, an emergency steroid card was provided. On follow-up after 8 weeks of treatment the patient showed significant improvement. Her weight increased by 7 kg, general wellbeing improved, menarche started, seizure controlled, and thyroid status became euthyroid. However, secondary sexual characteristics had not yet developed. The patient remains hypotensive but without postural drop. Her potassium level dropped. So, we kept hold of fludrocortisone and referred the patient to Bangladesh Medical University, Dhaka, Bangladesh.

Discussion:

The classical form of APS-1 is an autosomal recessive disorder caused by mutations in the AIRE gene (autoimmune regulator gene) found on chromosome 21. Mucocutaneous candidiasis, hypoparathyroidism, and Addison's disease form the three major components of this disorder. The diagnosis of APS-1 is usually made clinically when two of the three major component disorders are found in an individual patient. Siblings of individuals with APS-1 should be considered affected even if only one component disorder has been detected due to the known inheritance of the syndrome[6]. In our case, the patient had Addison's disease and hypoparathyroidism along with primary hypogonadism from this triad. Fahr's syndrome, secondary to autoimmune polyendocrine syndrome type 1, which includes adrenal insufficiency and mucocutaneous candidiasis in addition to hypoparathyroidism, is exceedingly rare. Only 1 case report has been documented to date to show Fahr's syndrome association with APS type 1. Nawaz A et al 2023[7] reported a 30-year-old Pakistani man with Fahr's syndrome as a manifestation of autoimmune polyendocrine syndrome-1 and its unusual association with neuromyelitis optica spectrum disorder. Our case is similar to the above-mentioned case in consideration of Fahr's syndrome confirmed by an MRI of the brain with and without contrast secondary to primary hypoparathyroidism confirmed by serum intact PTH and serum calcium. But the pattern of hypothyroid status is different. We found her thyroid status as like as central hypothyroidism; Serum TSH was 2.82 µIU/ml, serum FT4 was 6.97 pmol/L. The patient had been taking Carbamazepine 200 mg orally over the last 4 years. Kishlyansky and Kline 2021[8] reported a 24-year-old man with Bardet-Biedl syndrome (BBS) who was found to have isolated biochemical central hypothyroidism recognised as secondary to carbamazepine drug effect. In our case, there was no pituitary pathology in the MRI, and the replacement of carbamazepine by sodium valproate reversed the thyroid status to euthyroid S.TSH: 0.59 µIU/ml, FT4: 14.32 pg/ml.

Conclusion:

In Autoimmune Polyglandular Syndrome type 1 (APS-1), hypoparathyroidism, leading to low calcium levels, typically appears first, followed by adrenal insufficiency (Addison's disease). Fahr's syndrome, secondary to hyperparathyroidism, is a rare condition where a variety of presentation may occur. Among them, seizure management with carbamazepine increases the metabolism of both total and free T4 without raising S.TSH, so replacement of levothyroxine is not necessary; rather, replacement of carbamazepine is beneficial. There is no specific treatment to reverse the calcifications in Fahr's syndrome, but managing the

underlying cause (like hypoparathyroidism in APS-1) and addressing the symptoms can improve the patient's quality of life. Management of APS-1 should consider a multidisciplinary approach focusing on patient counseling, genetic counseling, hormone replacement, treatment of complication and regular follow-up because of varied presentation of the disease. Referral to a center with experience in the treatment of APS-1 is recommended.

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