Case Report

Acquired Hemophilia with Hypopituitarism

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Abstract

Acquired haemophilia is a rare haemorrhagic disorder which can present with mild to severe bleeding and can be potentially life threatening. Diagnosis of acquired haemophilia can be difficult because of the rarity of its presentation. It has been found to be associated with pregnancy, inflammatory bowel disease, hepatitis B and C, hypothyroidism and autoimmune disorders. We present the case of a 45 year old female patient with gum bleeding for two weeks with no family or personal history of a bleeding disorder. Further laboratory and radiological evaluation revealed a rare association of acquired haemophilia with hypopituitarism. Association of acquired haemophilia with hypothyroidism although by itself rare , is a known one, but acquired haemophilia with hypopituitarism (empty sella) is a rare one.

Key Words: Hypopituitarism, Acquired haemophilia, Coagulopathy , Empty sella, Prolonged aPTT.

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Introduction

Hypopituitarism is a partial or complete insufficiency of one or more anterior pituitary hormones which can be congenital or acquired. The prevalence of hypopituitarism was 46 cases per 1,00,000 individuals[1] which is most commonly associated with conditions such as postpartum pituitary necrosis (Sheehan's syndrome), radiation, post trauma, autoimmune hypophysitis and empty sella. Acquired hypopituitarism is associated with combined hormonal deficiencies like growth hormone, thyroid, cortisol, follicle stimulating hormone and leutinizing hormone. Although it is known that hypothyroid patients may have a decrease in von willibrand factor and Factor VIII levels[2], there are limited reports of hypopituitarism associated with factor VIII deficiency[3].

Case Report

A 45 yr old female patient, a known type II diabetic for 3 years was admitted with a history of spontaneous gum bleeding of 2 weeks duration with no similar previous episodes. There was no history of any other bleeding manifestations. She had no significant menstrual disturbances and her obstetric history was uneventful except for one spontaneous abortion in between the two normal deliveries. There was no bleeding disorder in the family. Patient is a betel nut chewer.

On examination, the patient was pale and with features of hypothyroidism. Patient had a poor oral hygiene with bleeding gums. Her vitals were normal. Examination of other systems did not reveal any abnormality.

Her haemoglobin was 5.6% and RBC 1.1 millions/cu.mm with normal leukocyte count and platelet count and peripheral smear revealed microcytic hypochromic anaemia. Her stool was negative for occult blood. Her creatinine was 1.4/dl, blood urea nitrogen of 22, sodium-129meq/L, potassium 3.6meq/L with fasting and posts prandial blood sugars, liver function tests normal. Thyroid functions confirmed a central cause for hypothyroidism (3-1.30pg/ml (2.5-3.9 pg/ml) 4-0.13ng/dl (.58-1.64ng/dl), TSH-3.03uiu/ml (0.34-4.6uiu/ml). Her viral markers for hepatitis were negative. The bleeding time, clotting time and coagulation profile were normal except for prolonged aPTT (29.2/23sec)

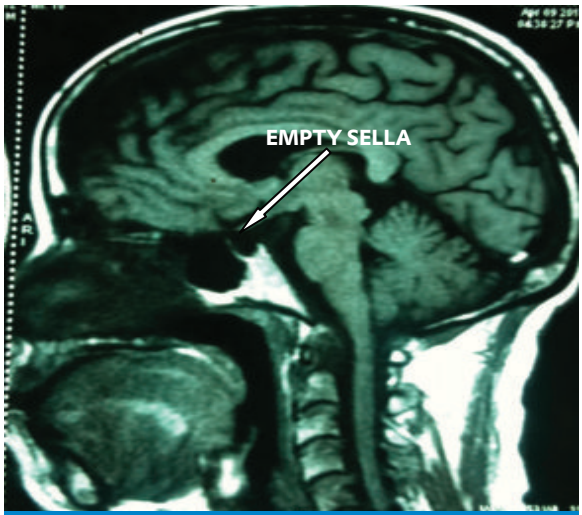

Fig1 – MRI : Empty sella with compressed and atrophied pituitary

MRI brain (Fig 1) was done to assess for the central cause of hypothyroidism which revealed a hematoma in the maxillary sinus and an empty sella with compressed and atrophied pituitary stalk. Serum cortisol levels at baseline (7.49) were compared with levels after insulin induced hypoglycaemic test (10.6). This confirms the presence of hypopituitarism. She was transfused 3 units of blood for anaemia. But bleeding persisted and repeat aPTT values after 5 days revealed a non coagulable serum and hence 2 units of cryoprecipitate was transfused. Repeat aPTT values were 28.5/24.9 (Test/Control).

Since the patient with no previous history of bleeding and isolated prolongation of aPTT, improved after 2 units of cryoprecipitate, clinically the diagnosis of acquired haemophilia was considered with von willibrands disease a close FVIII levels-35% (Normal 50-150%), normal VWF levels (>240), and ANA-negative. Mixing studies were done to distinguish between factor deficiency and presence of inhibitors to VIII. It showed prolongation of aPTT after 2hrs of incubation which confirmed the presence of inhibitors. Further confirmation requires FVIII inhibitor levels which is available only in specialized labs and hence could not be done. Thus the diagnosis of acquired haemophilia associated with hypopituitarism was made. Patient was treated with prednisone-60mg then slowly tapered to a dose of 10mg/day along with thyroxine 100 μg/day. At follow up, aPTT levels normalised after a period of 3 months and mild ooze present occasionally.

Discussion

Acquired haemophilia is a rare but potentially life threatening bleeding disorder with an incidence of 0.2-1 case per million per year 4[1] caused by the development of autoantibodies against plasma coagulation factors. Inhibitors to factor VIII is the most commonly observed abnormality and it may be associated with autoimmune disorders, pregnancy, inflammatory bowel disease, diabetes, hepatitis B and C, hypothyroidism and malignancies[4]. Few case reports show association with hypopituitarism[3].

Clinically patients present with acute or recent onset, persistent soft tissue or mucosal or muscle bleeds[5] and rarely cerebral haemorrhage and an isolated prolongation of aPTT as opposed to patients with congenital haemophilia who present early in life and have major bleeds into joints. Both can be differentiated using mixing studies[6]. Though not all patients present with typical symptoms of severe bleeding or aPTT prolongation, the diagnosis of acquired haemophilia should be considered and investigated properly. FVIII levels and FVIII inhibitors assay (Bethesda Assay) are the confirmatory tests.

Tests to assess the etiology includes, assay of various anterior pituitary hormones at baseline and after stimulation (Insulin Induced Hypoglycaemic test and ACTH stimulation test) which establishes the diagnosis of Hypopituitarism. Imaging studies will aid in confirming the diagnosis.

The treatment goals include -

1. control of bleeding episodes
2. eradicate inhibitors with immunosuppressive agents
3. treat the underlying disease

The treatment option for persistent mild bleeding includes factor VIII concentrates and/or desmopressin[7]. For major bleeding episodes and high inhibitors titres Activated protein complex concentrate(APCC), Factor VIII bypassing agents (FEIBA) and recombinant activated Factor VII (FVIIa) are used. Other strategies to control bleeding are to remove the inhibitors with plasmapheresis and immunoadsorption of the inhibitors to staphylococcal protein A or polyclonal sheep antibodies[8]. For eradication of the inhibitors, treatment was initiated with prednisone (1mg/kg/day) and cyclophosphamide (1.5-2 mg/kg/day) for a period of 5 weeks. Rituximab (anti CD-20) has recently shown effective eradication of the inhibitors as a second line of therapy[9]. Adequate replacement of the defective pituitary hormones[1] is the mainstay of therapy. Appropriate thyroxine replacements and steroids has shown to improve the factor VIII levels and decrease bleeding as in our case.

Conclusion

Thus a rare association of acquired haemophilia with hypopituitarism is established. Diagnosis of this rare disorder should be considered in patients with unexplained persistent and profound bleeding from soft tissues and mucosa, with a prolonged aPTT and signs of pituitary hormonal deficiency. Prompt identification and treatment of the underlying condition is of utmost importance to avert a potentially life threatening bleeding.

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திருக்குறள் 948

நோய்நாடி நோய்முதல் நாடி அதுதணிக்கும்
வாய்நாடி வாய்ப்பச் செயல்

மு.வ உரை:
நோய் இன்னதென்று ஆராய்ந்து, நோயின் காரணம் ஆராய்ந்து, அதைத் தணிக்கும் வழியையும் ஆராய்ந்து, உடலுக்கு பொருந்தும் படியாகச் செய்யவேண்டும்.

Couplet 948
Disease, its cause, what may abate the ill: Let the physician examine these, then use his skill.

Explanation
Let the physician enquire into the nature of the disease, its cause and its method of cure and treat it faithfully according to medical rule.