Congenital factor VII deficiency in Hirschsprung disease patient, a novel case report

Galila M. Zaher a, Jummanah S. Jarullah b,*, Soheir S. Adam a, Mazen O. Kurdi a, Mohammad Sarwar Jamal b, Ghazi A. Damanhouri a, b

a King Abdulaziz University Hospital, King Abdulaziz University, Jeddah, Saudi Arabia
b Hematology Research Unit, King Fahd Medical Research Centre, King Abdulaziz University, Jeddah, Saudi Arabia

1. Introduction

Hirschsprung Disease (HD) is a development disorder of enteric nervous system which is characterized by aganglionic intestine at Auerbach plexus and Meissner pleus area. Pathogenesis of HD is still not fully understood, however various hypothesis are proposed. Multiple congenital abnormalities are present in approximately 30% of patients. HD is genetically heterogeneous, with twelve genes involved so far [1]. The RET proto-oncogene on chromosome 10q11 is the major disease causing gene for non syndromic HD. Mutations in RET gene are responsible for 50% of familial HD cases and 15–20% of sporadic cases. HD has been associated with several chromosomal abnormalities and monogenic conditions, including trisomy 21, Mowat–Wilson, Smith Lemli–Opitz and Goldberg–Shprintzen syndromes [2]. Hirschsprung disease is also associated with SOX10 mutations. Hirschsprung disease appears to have a dominant pattern of inheritance, with incomplete penetrance.

Factor VII is one of the coagulation proteins involved in blood clotting. Factor VII deficiency is a congenital coagulopathy occurring at prevalence rate of 1:500,000. It has an autosomal recessive pattern of inheritance. Factor VII deficiency can also be acquired due to antibiotic, vitamin K deficiency and liver disease.

Hirschsprung disease, congenital megacolon disease is treated surgically. However, surgical correction has always been considered as a hemostatic challenge and in presence of congenital Factor VII deficiency, risk of bleeding is compounded. The co-occurrence of Hirschsprung disease (HD) and Factor VII in the same person is very rare.

2. Case report

This study was conducted at the King Abdulaziz University, Jeddah, Saudi Arabia. Prior to the start of the study an informed written consent was taken from the patient according to Helsinki declaration. The consent letter is attached in the manuscript file. The study was also approved from ethical committee of the King Abdulaziz University.

A 2 years old female was admitted to King Abdulaziz University Hospital (KAUH), with history of Hirschsprung disease. She was born by spontaneous vaginal delivery (SVD) at full term in another hospital. At the 1st day of life she had acute abdominal distension, which deteriorated on the second day to develop perforation. A
laparotomy was performed and she was found to have multiple perforations. She had excessive bleeding post operative and required blood transfusion. Resection of the segment with multiple perforation of the part of bowel was done and exteriorization of both proximal & distal part of the colon was done as well. The patient was stabilized with colostomy tube and referred to the pediatric surgery clinic at KAUH. She was the product of SVD, and there was no similar family history. On physical examination the child was malnourished and underweight with signs of infection on the colostomy site. Following improvement of the nutritional status of the patient, surgical correction was planned. Standard preoperative laboratory tests were obtained. She was found to have isolated prolongation of prothrombin time (PT) of 29.4 (reference range 11–14), Elevated International Normalized Ratio was 2.5 (reference range 0.8–1.3), a normal activated partial thromboplastin time (APTT) of 31.5 s (Reference range 29–40) and platelet count of 363 (reference range 150–450 *10^9/L). Factor VII was 8.3% (Reference range 70–120%). (Table 1).

Mixing study and Factor VII level confirmed the presence of Factor VII deficiency. Other causes of acquired FVII deficiency including liver disease, vitamin K deficiency were excluded. The parents were non-consanguineous and factor VII levels were below normal range for both parents (44% in the father and 39% in the mother), consistent with heterozygote state. There is no history of abnormal bleeding in the family.

Hemostasis was maintained by giving Factor VII concentrate, aiming for 50% correction before surgery. During surgery, swenson’s pullthrough was done. There was no excessive bleeding and tissue biopsy confirmed Hirschsprung disease. Post operative intravenous Recombinant factor VII was given every 4–6 hourly to maintain at the range of 40–70% for 5 days.

During post operative care there was no evidence of excessive bleeding from colostomy tube drains. On day 5 patient was conscious and receiving normal oral nutrition and she was sent home. Patient was followed up in both haematology and surgical clinic with no new complaints and she was gaining weight.

3. Discussion

Hirschsprung disease (HD)(MIM # 142623) is an intestinal congenital gut motility disorders affecting one in every 5000 live births, with fourfold male dominance [3]. Detailed study of prevalence of HD in Europe has shown that the incidence of HD recorded in 1980 (1.04 per 10,000) is increased in 2009 (1.42 per 10,000) with male to female ratio of 2.8:1. The increase in prevalence can be attributed to progress in the diagnostic tools. Prevalence studies for HD carried out in United states, United Kingdom and Columbia was between 1.63 and 2.26/10,000 live birth [4]. Amiel and Moore have shown that HD varies from 1.5 in Caucasians to 2.8 in Asians for every 10,000 newborns [2,5]. In Saudi Arabia, HD was reported in 27 cases of which 66.7% were male and 33.3% were female. The mean age of presentation was 3 months [6]. Another retrospective studies on congenital malformation of gastrointestinal tract carried out in Saudi Arabia, have documented incidence of HD of 1% (14cases) out of total 1386 cases [7].

HD has complex pattern of inheritance, which describes sex dependent penetration with 10 genes and 2 loci involved, of which tyrosine kinase receptor is the major gene. The most frequent genetic impairment is in rearranged during transfection (RET) proto-oncogene and endothelin receptor B (ENDRB) gene [8]. In 90% of the patients HD is diagnosed by delayed passage of meconium, while some cases are diagnosed later in life due to chronic constipation. HD may be either short aganglionic (S-HSCR) mostly in sigmoid colon, long aganglionic (L-HSCR) segment or total colonic aganglionosis (TCA). Expression of HD in a set of monozygous with HD, born to unrelated Arab parents, showed autosomal dominant gene with incomplete penetration.

The factor VII deficiency was simultaneously observed in the same patient. The combination of two rare diseases is unusual. Factor VII plays a fundamental role in coagulation cascade and its deficiency is rare with the incidence of 1 in 500,000 [9]. It is characterized by molecular and clinical heterogeneity and has an autosomal recessive pattern of inheritance. Factor VII gene is located on chromosome 13 and is 13 kb in size, 2.8 Kb upstream of Factor x gene. Deficiency of Factor VII can range from mild to most severe bleeding episode due to clinical heterogeneity attributed to different mutations. Treatment options include; plasma derived FVII concentrates and recombinant activated FVII (rFVIIc) as per guidelines for the management of FVII deficiency. (Australian, WHF).

A retrospective study over 8 years on hereditary bleeding disorders in Riyadh, Saudi Arabia included 168 patients of which only one had VII deficiency [10]. Furthermore another retrospective study from the western region of Saudi Arabia over 11 years reported the prevalence of inherited bleeding disorders reported one case of factor VII deficiency [11].

Consanguineous marriages are the root cause of high incidence of congenital defects in Saudi Arabia.

4. Conclusion

This case report describes a rare novel of congenital factor VII deficiency and Hirschsprung Disease in same patient. Hirschsprung disease was successfully corrected without excessive bleeding by maintaining an appropriate hemostatic level of factor VII, preoperatively and postoperatively. Epidemiological study in Saudi Arabia could provide insight of both these disorders, considering the high rate of consanguinity.

Conflict of interest

The authors declare that there is no conflict of competing interests for financial or non-financial, professional or personal.

---

Table 1

<table>
<thead>
<tr>
<th>Test</th>
<th>Patients</th>
<th>Mother</th>
<th>Father</th>
<th>Normal reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTa</td>
<td>29.4</td>
<td></td>
<td>12.4</td>
<td>11–14 s</td>
</tr>
<tr>
<td>APTTb</td>
<td>31.5</td>
<td>30</td>
<td>32</td>
<td>29–40 s</td>
</tr>
<tr>
<td>Platelets count</td>
<td>363 × 10^9/L</td>
<td>400 × 10^9/L</td>
<td>350 × 10^9/L</td>
<td>150–450 × 10^9/L</td>
</tr>
<tr>
<td>Inhibitor screen</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate</td>
<td>12.5</td>
<td>8.3%</td>
<td>39%</td>
<td>70–120%</td>
</tr>
<tr>
<td>Post-incubation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor VII level</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Prothrombin time.
b Activated Partial Thromboplastin Time.
Acknowledgement

We are thankful to King Abdulaziz University to provide us the facility to conduct this work and all the participants of this study. There was no fund to support this study.

References