A RARE CASE OF HAEMOPHILIA-A IN A GIRL

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Abstract: Evaluation of a 5 years old girl who presented with hemarthrosis, revealed Haemophilia-A. Many of her male family members had a bleeding disorder, presumably haemophilia-A. Her fathers factor VIII levels were 1. Analysis of the pedigree chart showed, she might have inherited the disease from her parents, father expressing the disease and the mother being a carrier. Females can manifest an X-linked recessive disease as a consequence of four different phenomena 1. Two mutant genes, homozygous or doubly heterozygous 2. One mutant gene plus extreme or non-random X chromosome inactivation (lyonisation), 3. Mutant gene plus XY genotype manifesting as a female and4. Chromosomal abnormality. Consanguineous marriages should be avoided in her family to prevent further dissemination of the disease. This case is presented for the rarity of X-linked recessive disease manifesting in a female and to highlight the importance of genetic counseling in a family with a hereditary disease.

Keyword: Haemophilia-A, X-linked recessive, consanguinity, female, Factor VIII.

CASE HISTORY:
A 5 years old female child, born to 2nd degree consanguineous parents, presented to us with the complaints of her left knee swelling for the past 2 days following a trivial injury. In the past history, she had minor bleeding in the form of ecchymosis at the injection site following vaccination in her infancy. At that time the ecchymosis resolved spontaneously without any treatment. On further probing the family history, her mother said many of her family members were suffering from bleeding disorder. So we evaluated this patient for bleeding disorder. Her platelets were normal in number and morphology. Bleeding time & prothrombin time were normal. aPTT was prolonged. Her factor VIII activity was <1%. So we diagnosed her to have haemophiliaA. Since then she is having Factor VIII replacement therapy for her bleeding episodes. Mutation studies to determine whether this girl had inherited the gene from her parents or if the disease
was due to a new mutation is not possible in a resource limited setting like ours.

Haemophilia-A being a very rare disease in females (1 in 100,000,000), we evaluated her two sisters as well. The factor VIII level of her older sister aged 16 years was in the mild haemophilia range. The younger sister aged 13 years old had a factor VIII activity in the carrier range.

Many of her male relatives were said to have a bleeding disorder. Her father is a known case of Haemophilia-A and his factor VIII level was <1% and he succumbed to uncontrolled bleeding after a head injury. As we wanted to trace the family pedigree to a few more generations, we felt it will be apt to talk to the eldest member in the family. So we visited the girl’s house and interacted with her grandmother who is now about 75 years old. The grand mother gave us a family history up to 3 generations. The detailed pedigree chart is enclosed below for easy reference (The details of unaffected family members were not shown in detail for want of space).

In the pedigree chart, we saw ten of her male family members had a bleeding disorder. Of these ten males, six succumbed to death due to uncontrolled bleeding. The remaining four males were fully evaluated and their Factor VIII levels were below 1%. There were about ten female carriers evident in the pedigree chart. Her mother, who is about 40 years old, is not having any bleeding manifestations and her factor VIII level is in carrier range.

**DISCUSSION:**

Haemophilia-A is an inherited, X-linked recessive disorder caused by deficiency of functional plasma clotting factor VIII (FVIII). Significant rates of spontaneous mutation and acquired immunologic processes can result in this disorder as well. Haemophilia-A is the most common form of inherited bleeding disorder, present in about 1 in 5,000–10,000 male births.

Haemophilia-A usually occurs in males (1 in 10,000) and less often in females (1 in 100,000,000). An affected female can be born out of an affected father and a carrier mother, though the Mendelian frequency for such a situation is approximately 1 in 50 million female births.

Haemophilia has featured prominently in European royalty and thus is sometimes known as “the Royal disease”.

Laboratory studies for suspected haemophilia include a complete blood cell count, coagulation studies, and a factor VIII assay.

The treatment of haemophilia involves achieving haemostasis, management of bleeding episodes, use of factor replacement products and medications, management of patients with factor inhibitors as a consequence of repeated factor VIII transfusions, and prevention, treatment and rehabilitation of patients with hemophilia synovitis.

**Classification:**

A Haemophilia-A carrier on an average has half the normal activity of Factor VIII.
Genetics of haemophilia:
Classical undergraduate teaching is that Haemophilia-A is an X-linked recessive disease that manifests only in male siblings with females as the carriers. However, a deeper analysis of medical literature suggests that X-linked recessive disease can also manifest in females.

Haemophilia-A is inherited through X-linked recessive pattern. Females possess two X-chromosomes, males have one X and one Y-chromosome. Since the mutations causing the disease are X-linked, a woman carrying the defect on one of her X-chromosomes may not be affected by it, as the equivalent allele on her other chromosome would express itself to produce the necessary clotting factors. However, the Y-chromosome in men has no gene for factors VIII. If the genes responsible for production of factor VIII are deficient on a male's X-chromosome, there is no equivalent on the Y-chromosome to negate it, so the deficient gene is not masked and he will manifest the illness (Fig:1).

<table>
<thead>
<tr>
<th>Mild</th>
<th>5-50%</th>
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<tbody>
<tr>
<td>Moderate</td>
<td>1-5%</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;1%</td>
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X- Normal (unaffected) gene x- Defective gene XX- Unaffected female XY- Unaffected male Xx- Carrier female xY- Affected male xx- Affected female Since a male receives his single X-chromosome from his mother, the son of a healthy female silently carrying the deficient gene will have a 50% chance of inheriting that gene from her and with it the disease; and if his mother is affected with haemophilia, he will have a 100% chance of being a haemophiliac. In contrast, for a female to inherit the disease, she must receive two deficient X-chromosomes, one from her mother and the other from her father (who must therefore be a haemophiliac himself). Hence haemophilia is far more common among males than females. However, it is possible for female carriers to become mild haemophiliacs due to lyonisation (inactivation) of the X-chromosomes. Haemophiliac daughters are more common than they once were, as improved treatments for the disease have allowed more haemophiliac males to survive to adulthood and become parents. Adult females may experience menorrhagia due to the bleeding tendency. A mother who is a carrier has a 50% chance of passing the faulty X-chromosome to her daughter, while an affected father will always pass on the affected gene to his daughters. A son cannot inherit the defective gene from his father. Genetic testing and genetic counseling is recommended for families with haemophilia. Prenatal testing, such as amniocentesis, is available to pregnant women who may be carriers of the condition. As with all genetic disorders, it is also possible for a human to acquire it spontaneously through mutation, rather than inheriting it, because of a new mutation in one of their parents' gametes. Spontaneous mutations account for about 33% of all cases of haemophilia A. If a female gives birth to a haemophiliac child, either the female is a carrier for the disease or the haemophilia was the result of a spontaneous mutation. If an affected male marries a female carrier, then his daughters will be affected or will be carriers of haemophilia. 50% of his sons will not be affected with the disease and 50% will be normal. The disease is X-linked and the father cannot
pass haemophilia through the Y-chromosome (Fig:2).

X- Normal (unaffected) gene x- Defective gene XX- Unaffected female XY- Unafficted male Xx- Carrier female xY- Affected male xx- Affected female

<table>
<thead>
<tr>
<th>Normal Father</th>
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<th>y</th>
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<tbody>
<tr>
<td>Carrier Mother</td>
<td>x</td>
<td>xx</td>
</tr>
<tr>
<td></td>
<td>x</td>
<td>xx</td>
</tr>
</tbody>
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Ways that a male can have hemophilia:
- A hemophilic father or a carrier mother
- A mutation in the germ-line of either parent
- A mutation in the zygote (early embryo) herself

III. ONE MUTANT GENE PLUS XY

<table>
<thead>
<tr>
<th>Affected Father</th>
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<th>y</th>
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<tbody>
<tr>
<td>Carrier Mother</td>
<td>x</td>
<td>xx</td>
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X- Normal (unaffected) gene x- Defective gene XX- Unaffected female XY- Unaffected male Xx- Carrier female xY- Affected male xx- Affected female

Ways that a female can have hemophilia:
- Two mutant genes, homozygous or doubly heterozygous -hemophilic father and carrier mother -hemophilic father and mother with a new germ-line mutation -carrier mother and a normal father with a new germ-line mutation -normal parents, both new germ-line mutations

II. ONE MUTANT GENE PLUS EXTREME OR NON-RANDOM X- CHROMOSOME INACTIVATION (LYONISATION),

MUTATIONS:
The factor VIII gene has relatively little normal variation from one person to the next. However, the variety of mutations causing haemophilia-A is rich. Over a thousand distinct mutations have been reported in different patients with haemophilia-A.
The major types of mutations are as follows.

Missense mutation

Nonsense mutation

Insertions, deletions

Splice site mutations

Inversions

Loss-of-Function, Gain-of-Function mutation

CONCLUSION:
Since this girl and her sisters are the children of a haemophiliac father and his first cousin, this unusual occurrence of affected female members in a haemophiliac family can be explained by assuming that their mother was a carrier, and that they were homozygous for the disease. Eventhough a new mutation cannot be ruled out in this girl, it can be logically assumed that she has inherited the disease from both her parents because of consanguinity. Here genetic counseling will play a major role in preventing the transmission of the disease to the next generations. Simple avoidance of consanguineous marriage in their family will help in that. We had appraised this fact to all her family members by showing the pedigree chart. The family members accepted our counseling and said that they will avoid consanguineous marriage in future.

References:

2 The occurrence of Haemophilia in the human female, by Clarence Merskey;

Quarterly Journal of Medicine, New Series XX, No. 79, Jury 1951.

