Factor XIII deficiency in Sistan and Baluchestan of Iran

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OBJECTIVES

Coagulation factor XIII is the last factor of the coagulation cascade; however, presents at all coagulation stages. This zymogene exists in plasma as tetramer which consists of two 'Activator' subunits and two B carrier subunits(A2B2).
Factor XIII has an important role in wound healing and tissue regeneration ([5]). In addition, the factor is required for maintaining safe pregnancy ([7]). Maternal A subunits locates in placenta, where it has a key role in trophoblastic cortex formation and Nitabuch layer. Factor XIII deficiency leads to weak formation of cytotrophoblastic cortex and fibronoid layer whichin turn results in separation of the placenta from the uterus.
Severe congenital factor XIII deficiency was initially described by Duckert et al. in 1960. This factor has got the longest half-life compared with all other coagulation factors; and as soon its action decreased to one percent or less, the clinical symptoms would emerge. Coagulation tests (including PT, PTT, TT) are normal in patients with factor XIII deficiencies, whereas the patients' urea solubility test on 5 M and/or one present citric acid is abnormal. Definitive diagnosis established by ELISA and the measurement of functional activity.
Treatment with FXIII concentrate would result in the re-establishment/retrieval of normal coagulation patterns in these patients. Relapse/reversion rate in patients who do not receive appropriate prophylaxis is very high. Bleeding had also been observed from the mucous membranes and during operation/surgery. Other pharmaceutical products to combat FXIII deficiency include Fresh-Frozen plasma(FFP) and Cryoprecipitate (CP); however, these products are not recommended mainly due to the transmission of infectious blood products which may cause other patients at risk of getting diseases such as HIV/AIDS or HBV.
As this disorder is autosomal recessive, it is believed to be more common in populations with a high rate of consanguinity, such as the populations of Sistan and Baluchistan . Up to December 2011, we had registered a total of 213 FXIII-deficient from 92 unrelated families. This study aims to provide a new and quick way to diagnose the disease based on the patients' clinical manifestation such as delayed wound healing, umbilical bleeding and recurrent abortions. In total, 200 patients were selected to participate in this study. The patients were divided into two receiver and non-receiver prophylaxis groups, so in this study we investigate the clinical manifestation of this in disease patient referred to the Ali Asghar and Ali Ibn Abi Taleb hospital.

METHODS

Material and Method
Methods of data collection
To extraction of Patients required information, we used from congenital factor XIII deficiency records in Sistan and Baluchistan and its information recorded.
Methods
All known cases of patients with factor XIII deficiency after signed informed consent in this province were assessed. Extracted data from them and was recorded and then the obtained data were evaluated clinically and various manifestation in these patients was determined. The sample size including All cases of congenital factor XIII deficiency in mentioned province that have 200 patients and with census method are enrolled at the end of study, extracted data analyzed (considered)by statistical methods such as mean, frequency and standard deviation by using SPSS ver. 17 software.

Table 4-1.Frequency distribution of intracranial and extracrainal hemorrhage in patients with congenital factor XIII deficiency

intracranial hemorrhage	Number	Percent (%)	Number	Percent (%)
Yes	33	16.1	17	8.3
No	172	83.9 5	188	91.7
Total	205	100	205	100

Table 4-2. Frequency of congenital factor XIII deficiency in patients with cord blood

Umbilical cord bleeding	Number	Percent (%)
Yes	173	84.4
No	32	15.6
Total	205	100

Table 4-3. Frequency of congenital factor XIII deficiency in patients with a history of abortion in women

The history of abortion on pregnancy age	Number	Percent (%)
Yes	7	9.8
No	64	90.1
Total	71	100

Table 4-4.Frequency distribution of factor XIII deficiency based on the agein Sistan and Baluchistan province.

Age (years)	Number	Percent (%)
<5	46	22.4
5-10	58	28.3
10-15	32	15.6
15-20	28	13.7
>20	40	19.5
Total	205	100

Table 4-5. Frequency distribution of factor XIII deficiency based on the sex in Sistan and Baluchistan province.

Sex	Male (N)	Female (N)	Total (N)	p-value
<5	18	28	46	0.151
5-10	30	28	58	
10-15	13	19	32	
15-20	60	11	28	
>20	19	21	40	
Total	97	107	204	

RESULTS

Re sults
The frequency distribution of intracranial and extracranial hemorrhage in patients with congenital factor XIII deficiency.
Analyzed data indicate that, 33 patients (16.1%) have intracranial hemorrhage and 172 patients (89.3%) had no intracranial hemorrhage. .In this study, 17 patients (8.3 %) had extracranial and 188 cases (91.7 %) had no extra-cranial hemorrhage (Table 4-1).
The frequency of congenital factor XIII deficiency in patients with umbilical cord bleeding (hemorrhage).
In this study, 173 patients (84.4 %) had umbilical cord bleeding and 32 patients (15.6 %) had no umbilical cord bleeding. (Table 4-2 and Table 4-3).
The frequency of congenital factor XIII deficiency in patients with a history of abortion in women
Among of women on childbearing age (pregnancy period) in 15 until 49 years, 7 patients (9.8 %)had a history of abortion and 64 (90.1 %) had no history of abortion.(Table 4-3 and Table 4-4).
Frequency distribution determination of Factor XIII deficiency based on the age in Sistan and Baluchistan province.
Of the 205 patients studied, 46 patients (22.4 %) were under 5 years, 58patients (28.3 %) had between 5 to 10 years, 32 patients (15.6 %) had between 10 to 15 years, 28 patients (13.7 %) had between 15 to 20 years and 40patients (19.5 %) had over 20 years.
Frequency distribution determination of Factor XIII deficiency based on the sex in Sistan and Baluchistan province.
In this study, 98 patients (47.8 %) male and 107 (52.2 %) were female. (Table 4-5)
Table 4-5. Frequency distribution of factor XIII deficiency based on the sex in Sistan and Baluchistan province.
In this study, 35patients with factor XIII deficiency that had intracranial hemorrhage were studied. The mean age of the 35 studied patients was 15.8±8.8 years (3-35 years-old). And mean age in females 14.6±9.7 years (3-30 years-old), and in males was 17.1±7.8 years (6-35 years-old) (p=0.416).). It should be noted that 2 patients (5.7%) [2 females] were in the age group less than 5 years-old, 8 patients (22.9%) [3 males, 5 females] 5 to 10 years-old, 6 patients (17.1%) [3 males, 3 females] 10 to 15 years-old, 8 patients (22.9%) [6 males, 2 females] 15 to 20 years-old, and 11 patients (31.4%) [5 males, 6 females] had more than 20 years-old (p=0.273).Of 35 studied patients, 17 patients (48.5%) males and 18 patients (51.5%) were female (p=347).

CONCLUSIONS

Conclusion
Factor XIII deficiency is a rare bleeding disease.Its prevalence is 1 in 3 million in the worldwide .Reports about this disease, it has been very limited so that for example the number of known cases in Britain is 26 cases and the most comprehensive study which performed by the European coagulation disease research organization, is72in 1996.
The mean age of patients are 12.7±8.4 years and the 205 studied patients were46 patients (22.4 %) were under 5 years, 58patients (28.3 %) between 5 to 10 years, 32 patients (15.6 %) between 10 to 15, 28patients (13.7 %)between 15 to 20 years and 40 patients (19.5 %) over 20 years which Indicating the high prevalence of the disease at an early age and also represents high power identification of this disease.
In this study, 35 (16.1 %) had an intracranial hemorrhage. The incidence of intracranial hemorrhage in this disease, are more than other bleeding disorders. In addition, there are reports that indicate a very probability of occurrence of these events, onset 3 months which express rapid diagnosis is essential.
Present of clinical manifestation, such as umbilical cord- bleeding, abortion, intracranial and extra-cranial hemorrhage can provide rapid and timely diagnosis of this disease. In our study, 173 patients (84.4 %) have cord hemorrhage and 17 patients (8.3 %)have extra-cranial hemorrhage. Among women of childbearing age (pregnancy period) between 15 to 49 years, 7 patients (9.8%) had a history of abortion. Between intracranial hemorrhage and abortion was significantly associated with age (05 / 0> p).
Considering the results of this study and the high rate of consanguineous marriage in this state and the normalization of all coagulation tests, platelet count and function, so by using clinical manifestation of patients can helpful as a way to faster diagnose.
In our study, affection status of first-degree family members of studied patients and their survival status (alive, certain death resulting from FXIII deficiency disease, suspicious deaths primarily associated with FXIII deficiency disease/ or unknown causes) were included: non-affected sister/ or brother, and no suspicious/ or certain death primarily associated with the disease in family members of 8 studied patients (22.8%) [2 males, 6 females], alive brother / and or sister with FXIII deficiency disease in 6 patients (17.1%) [1 male, 5 females] brother / and or sister with suspicious deaths primarily associated with FXIII deficiency disease/ or unknown causes in 9 patients (25.7%) [6 males, 3 females], alive brother / and or sister with FXIII deficiency disease + brother / and or sister with suspicious deaths primarily associated with FXIII deficiency disease/ or unknown causes in 2 male patients (5.7%), brother / and or sister with certain death resulting from FXIII deficiency disease in 4 patients (11.6%) [2 males, 2 females]; and 6 patients (17.4%) [4 males, 2 females] had brother / and or sister with certain death resulting from FXIII deficiency disease + brother / and or sister with suspicious deaths primarily associated with FXIII deficiency disease/ or unknown causes (p=0.301).
About the deaths of family members of studied patients was 44 cases; that 10 cases (22.7%) [4 brothers, 6 sisters] had certain death resulting from FXIII deficiency disease, 20 cases (45.5%) [10 brothers, 10 sisters] suspicious deaths primarily associated with FXIII deficiency disease; and in 14 cases (31.8%) [5 brothers, 9 sisters] cause of death was unknown (p=0.607)

REFERENCES:

References
1- Karimi M, Bereczky Z, Cohan N, Muszbek L. Factor XIII deficiency. Semin Thromb Hemost 2009;35:426-438.
2- Muszbek L, Bagoly Z, Bereczky Z, Katona E ´. The involvement of blood coagulation factor XIII in fibrinolysis and thrombosis. Cardiovasc Hematol Agents Med Chem 2008;6:190–205.
3- Ichinose A. Physiopathology and regulation offactor XIII. Thromb Haemost. 2001;86:57-65.
4- Koseki-Kuno S, Yamakawa M, Dickneite G, Ichinose A. Factor XIII A subunit-deficient mice developed severe uterine bleeding events and subsequent spontaneous miscarriages. Blood 2003;102(13):4410–2.
5- Dardik R, Loscalzo J, Inbal A. Factor XIII (FXIII) and angiogenesis. J ThrombHaemost 2006;4:19–25.
6- Muszbek L, Bagoly Z. Fibrin formation disorders and pregnancy loss. Thromb Res 2007;119(Suppl 1):S69–S70.
7- Anwar T, Miloszewski K. Factor XIII deficiency. Br J Haematol 1999;107:468–484.
8- Asahina T, Kobayashi T, Okada Y, Goto J, Terao T. Maternal blood coagulation factor XIII is associated with the development of cytotrophoblastic shell. Placenta 2000; 21(4):388–93.
9- Asahina T, Kobayashi T, Takeuchi K, Kanayama N. Congenital blood coagulation factor XIII deficiency and successful deliveries: a review of the literature. Obstet Gynecol Surv 2007;62:255–60.

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