International Journal of Medical Research Professionals
P-ISSN: 2454-6356; E-ISSN: 2454-6364
DOI: 10.21276/ijmrp

IJMRP

Case Report .

Protein C Deficiency: A Novel Presentation with Extended Family History

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ABSTRACT

Protein C is a blood factor that plays a key role in anti-coagulation processes which aim to maintain the circulatory homeostasis. A deficiency in this protein can be acquired by inheritable or sporadic routes. When inherited, protein C deficiency passes through generations in an autosomal dominant manner by (PROC) gene mutations. Its diagnosis is based on the clinical and laboratory findings. In this report, we present a case of protein C deficiency in a family who has an extended history of this disease in addition to a novel co-presentation of lower limb lipoma.

Key Words: Pediatrics, Neonatology, Hematology, Protein C, Lipoma.

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Article History:
Received: 12-12-2017, **Revised:** 04-01-2018, **Accepted:** 22-01-2018

Access this article online	
Website: www.ijmrp.com	Quick Response code
DOI: 10.21276/ijmrp.2018.4.1.068	

INTRODUCTION

Protein C is a vitamin-K dependent anti-coagulation factor that plays a major role in blood flow.[1] The deficiency in this protein is a relatively rare hereditary trait that leads to a thrombotic state which in turn predisposes to certain manifestations and complications at different ages.[2] This disease passes through generations in an autosomal dominant manner.[3-5] Until now, there are two phenotypes described in the literature: type 1 and 2.[5] In the first type, the disease occurs due to decreased amount of the protein in the blood and is most commonly caused by a missense or nonsense mutation.[4-6] These mutations can decrease the production of protein C or hasten its destruction.[4] On the other hand, type 2 is more related to the quality of the circulating factor.[7] The disease can be transmitted in inheritable or sporadic ways.[8,9] In cases of inheritance, the defect is mostly found in PROC gene that is located on the 2nd chromosome.[10] On the other hand, there are other determinant factors that cause acquired protein C deficiency such as DIC, liver diseases, and certain infections especially in meningococcemia.(9) In general, this protein deficiency is prevalent in 0.5% of the general population.[11] Regarding diagnosis, the vast majority of laboratories has set the threshold for deficiency below around 65 percent of normal values gained by using a given test and laboratory conditions.[12] Diagnosis is based on the clinical picture supported by the protein C level in the blood.[13] In this report, we present a hugely extended family history of protein C deficiency with a novel finding of lower limb swelling that is, for our best knowledge, described for the first time in the literature.

CASE PRESENTATION

This is a 6-month old girl of a family whose members are known to have protein C deficiency. She was delivered as a late preterm of 36+2 weeks by an emergent caesarean section due to foetal distress. Upon delivery, she had a birth weight of 2.685kg and an APGAR score of 8 at 1 minute and 9 at 5 minutes then transferred to nursery with a good condition. However, at the age of 12 hours of life, she developed jitteriness that was associated with desaturation, tachycardia, and seizures. Due to these events, the patient was transferred to the neonatal intensive care unit for observation.

Brain ultrasound and MRI were both evident of bilateral sub-ependymal haemorrhage that extends to the bilateral ventricular system in keeping with interventricular haemorrhage of grade 4 that resulted in hydrocephalus. For jitteriness, electro-encephalogram showed severe seizure disorder, for which started her on phenobarbitone.

Ophthalmic examination showed retinal haemorrhage. At the same time, blood work-up revealed a derangement of the coagulation as the initial protein C level was less than 5.8%, INR of 1.6, prothrombin time of 20, partial thromboplastin time of 59, fibrinogen of 0.39, d-dimers of 18.07, and a platelet count of 68. Thereafter, she received fresh-frozen plasma.

Prenatal history was insignificant except for that the mother received LMWH during pregnancy to decrease the risk of hypercoagulability state as she is a carrier of protein C deficiency with recurrent history of abortions. The family history is apparently

remarkable for a huge number of affected individuals. Among the family members, the children are noted to have an unusual presentation of lower limb swelling that starts at the age of 6 months.

FAMILY HISTORY

The father is married to two wives. He is consanguineous to both of them. (Figure 1) The first wife is G17P11,1+6. (Figure 2) In details, she has one healthy boy and nine affected descendants, three of whom passed away. Moreover, she had six abortions, one stillbirth, and one early neonatal death at the age of 2 weeks who is suspected to be affected too.

Regarding the second wife, she is G9P5+4.(Figure 3) Three of her children are affected with one daughter who is undiagnosed yet. Similarly, she had a history of 4 abortions and one neonatal death 2-hours after birth that is most likely due to the same disease.

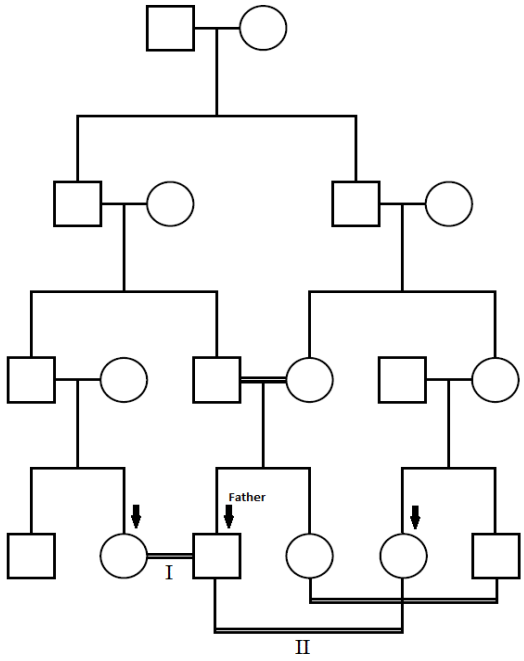

Figure 1: Shows the general family pedigree

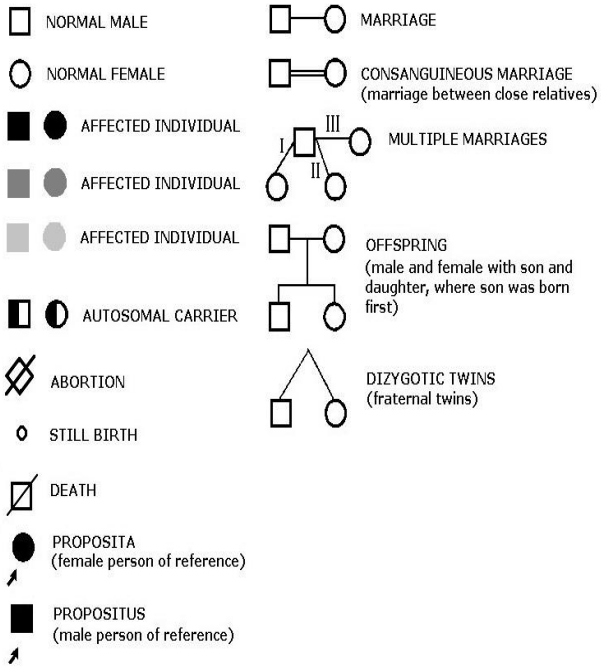

Table 1: Shows the pedigree illustrative symbols.

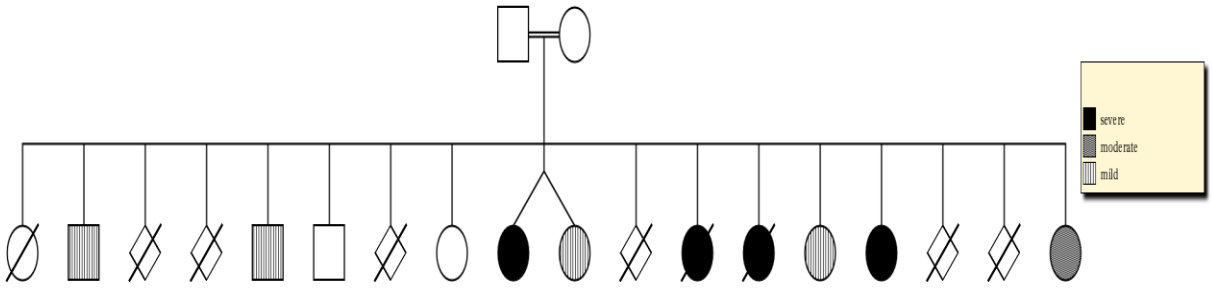

Figure 2: Shows the family pedigree of the patient's family (the first wife) with different disease severities.

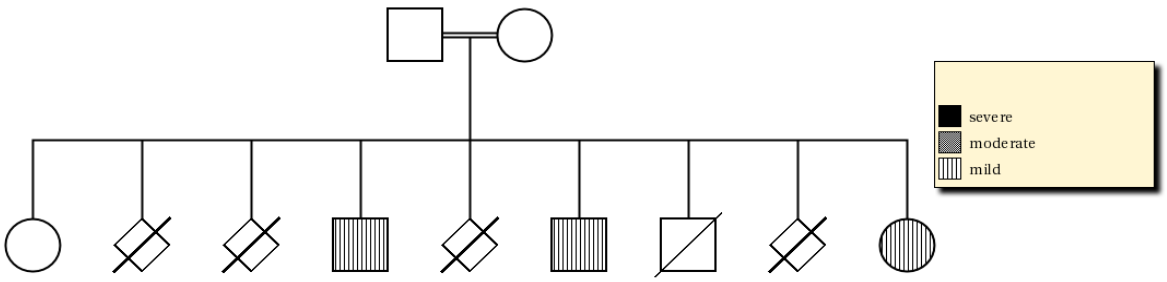

Figure 3: Shows the family pedigree of the second wife.

DISCUSSION

In neonatal period, protein C levels are variable and generally lower than in the adult population. However, other determinants for the severity of deficiency in this age are purpura fulminans and disseminated intravascular coagulopathy (DIC). In our case, there was a level of lower than 5.8 in additions to a state of (DIC).[14]

During the intrauterine phase, the fetus with protein C deficiency cannot receive extrinsic protein C from the maternal side since this protein does not cross the placenta. Thus, the high risk of thrombosis in these babies exposes them to perinatal intraventricular hemorrhage (IVH) and even blindness. After birth, the protein C levels start to increase until it peaks at the age of 2 years.[15]

The normal average protein C levels in healthy term infants are around 40IU/dL. This number increases as the child grows up until it reaches 60IU/dL around the age of puberty. In our case, the neonatal protein C level was 5.8%. In addition, the other family members have low levels of protein C that fluctuate from 20 down to zero.

The severity of protein C deficiency depends on its concentration in the blood. Mild form is defined as a level of more than 20 IU/dL. Moderate-severe deficiencies range between 1-20 IU/dL. In the most severe phenotypes, protein C levels decrease to lower than 1 IU/dL or, in some cases, to undetectable amounts.[15] In our patient, the level of protein C was 5.8% which falls within moderate-severe intensities. The other family members have fluctuating levels of protein C from mild to severe degrees with one reading that reaches to zero level.

Because of their accelerative physiological development, infants' protein C levels are rapidly changing over time. Thus, there is no specific neonatal range for protein C that is steadily reliable.[16,17]

Genetic testing was not performed yet for our patient. However, her older affected sister is supported with a genetic study that revealed c.1163 C>T (Ala388Val) defect. Upon our literature review, we could not find a previous documented similar mutation for protein C deficiency in other families.

Interestingly, this family, including descendants of both wives, has a large number of affected children. As one of the largest prevalence studies, this family has 8 affected and 7 carrier children. In addition, there is a history of 10 spontaneous abortions which are suspected to be related to the protein C deficiency too. Overall, there is only one healthy male.

As an unusual finding, we found a rare presentation in three affected children of the patient's family. After the age of 6 months, they started to have lower limb swelling that is mainly in the thighs and buttocks. It is associated with skin color changes to red and purple with pruritic sensation. These swellings were painful to the degree that leads to walking limitation. Markedly, it regresses after receiving protein C replacement doses. (Figure 4 A, B) show pictures for the older sibling with the apparent lipoma.

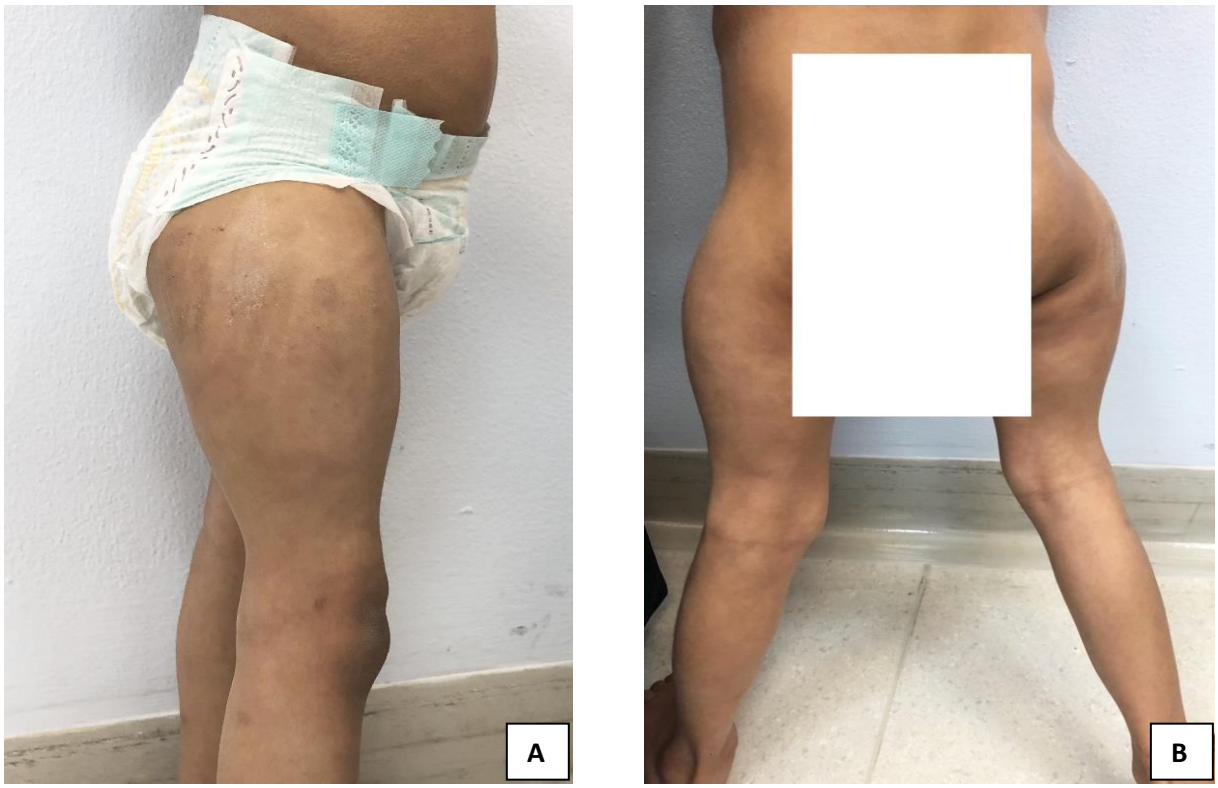

Figure 4 (A,B): shows two views of the older sibling. The thighs look mildly discolored with scratch marks. It appears less swollen after the last dose of protein C.

REFERENCES

1. Clouse LH, Comp PC. The regulation of hemostasis: the protein C system. N Engl J Med. 1986 May 15. 314(20):1298-304.

2. Griffin JH, Evatt B, Zimmerman TS, Kleiss AJ, Wideman C (1981). Deficiency of protein C in congenital thrombotic disease. J. Clin. Invest. 68 (5): 1370–3.

3. Reitsma PH. Protein C deficiency: from gene defects to disease. Thromb Haemost 1997; 78:344.

4. Reitsma PH, Bernardi F, Doig RG, et al. Protein C deficiency: a database of mutations, 1995 update. On behalf of the Subcommittee on Plasma Coagulation Inhibitors of the Scientific

and Standardization Committee of the ISTH. Thromb Haemost 1995; 73:876.
5. Reitsma PH, Poort SR, Allaart CF, et al. The spectrum of genetic defects in a panel of 40 Dutch families with symptomatic protein C deficiency type I: heterogeneity and founder effects. Blood 1991; 78:890.
6. Romeo G, Hassan HJ, Staempfli S, et al. Hereditary thrombophilia: identification of nonsense and missense mutations in the protein C gene. Proc Natl Acad Sci U S A 1987; 84:2829.
7. Lind B, Johnsen AH, Thorsen S. Naturally occurring Arg(-1) to His mutation in human protein C leads to aberrant propeptide processing and secretion of dysfunctional protein C. Blood 1997; 89:2807.
8. Inoue H, Terachi SI, Uchiumi T, et al. The clinical presentation and genotype of protein C deficiency with double mutations of the protein C gene. Pediatr Blood Cancer 2017; 64.
9. Mannucci PM, Vigano S. Deficiencies of protein C, an inhibitor of blood coagulation. Lancet. 1982;2(8296):463.
10. D'Ursi P, Marino F, Caprera A, Milanesi L, Faioni EM, Rovida E. ProCMD: A database and 3D web resource for protein C mutants. BMC Bioinformatics. 2007;8(Suppl 1):S11. doi:10.1186/1471-2105-8-S1-S11.
11. Tait RC, Walker ID, Reitsma PH, et al. Prevalence of protein C deficiency in the healthy population. Thromb Haemost. 1995;73(1):87.
12. Bovill EG, Bauer KA, Dickerman JD, et al. The clinical spectrum of heterozygous protein C deficiency in a large New England kindred. Blood 1989; 73:712.
13. Pabinger I, Allaart CF, Hermans J, et al. Hereditary protein C-deficiency: laboratory values in transmitters and guidelines for the diagnostic procedure. Report on a study of the SSC Subcommittee on Protein C and Protein S. Protein C Transmitter Study Group. Thromb Haemost 1992; 68:470.
14. Van Teunenbroek, A., Peters, M., Sturk, A. et al. Eur J Pediatr. 1990;149: 774
15. Mosnier LO, Zlokovic BV, Griffin JH. The cytoprotective protein C pathway. Blood. 2007 Apr 15;109(8):3161-72.
16. Andrew M, Paes B, Milner R, et al. Development of the human coagulation system in the full-term infant. Blood 1987; 70:165.
17. Raffini L. Thrombophilia in children: who to test, how, when, and why? Hematology Am Soc Hematol Educ Program 2008:228.

Source of Support: Nil. **Conflict of Interest:** None Declared.

Cite this article as: Amal AlSaedi, Arwa AlYamani, Hamdan AlRajhi, Khalid AlGhamdi. Protein C Deficiency: A Novel Presentation with Extended Family History. Int J Med Res Prof. 2018 Jan; 4(1):323-26.DOI:10.21276/ijmrp.2018.4.1.068