

# Clinical and Laboratory Findings in Jewish and Bedouin Patients in Southern Israel Who Were Diagnosed with Factor VII Deficiency

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**ABSTRACT:** **Background:** Congenital factor VII deficiency is a rare recessive autosomal bleeding disorder with a wide spectrum of clinical manifestations.

**Objectives:** To compare the clinical and laboratory findings in Jewish and Bedouin patients with factor VII deficiency.

**Methods:** The clinical and laboratory findings of patients with factor VII deficiency treated at Soroka Medical Center, a tertiary hospital in Israel, from 2005 to 2015 were analyzed regarding blood factor levels, illness severity, treatment administration, and disease outcome.

**Results:** Seventy-eight patients were enrolled (1:13,000 of the population in southern Israel) of whom 26 were diagnosed with severe factor VII deficiency (1:40,000). Sixty (76.9%) patients were Jewish and 18 (23.1%) were Bedouin. In univariable analysis, Bedouin patients exhibited a more severe illness, with significantly higher complication and fatality rates, and required more preventive treatment than the Jewish patients.

**Conclusions:** The prevalence of congenital factor VII deficiency (including severe deficiency) in the Jewish and Bedouin populations of southern Israel is higher than previously reported. The clinical spectrum of the disease was found to be more severe in the Bedouin population.

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cal severity that correlate poorly with plasma factor VII level [3,4]. Severe bleeding is rare in patients with a factor VII blood level above 10% of the norm, although some patients who are asymptomatic have a very low blood level factor VII [5].

Common symptoms include menorrhagia (78%), epistaxis (58%), gum bleeding (38%), hemarthrosis (13%), gastrointestinal bleeding (17%), and intracranial bleeding (2%). Symptoms may range from few or none to life-threatening bleeding [6]. In heterozygous patients, most bleeding incidences occur after surgical procedures or during situations prone to bleeding, such as pregnancy [7].

Missense mutations tend to be less severe than deletions, nonsense, splicing, or promotor mutations, which can be life threatening [8]. Unlike most bleeding disorders, in factor VII deficiency, clinical manifestation can occur not only in homozygous mutations but also in compound heterozygous and heterozygous mutations. In fact, 20% of those with heterozygous mutations show symptoms [6].

Laboratory findings distinguish between prolonged prothrombin time (PT) and normal partial thromboplastin time (PTT). However, cases of mild or moderate factor VII deficiency can result in normal PT and PTT, demonstrating the importance of measuring the blood factor levels.

Because of the variability of the condition, early diagnosis is important for newborns in families with a known history of severe deficiency. Thus, it is imperative to have an understanding and grasp of the prevalence of the disease in the general population, specifically in the Bedouin population. This population group, due to high levels of consanguinity, seems to be more symptomatic.

Factor VII deficiency is treated by administration of products containing activated factor VII, such as recombinant FVII or factor VII concentrates [9–11]. These supplements have been shown to be efficient, although they increase the risk of thrombosis. If such products are not available, fresh frozen plasma can be administered. However, the short half-life time (2–8 hours)

Congenital factor VII deficiency is a rare autosomal recessive bleeding disorder [1]. Factor VII deficiency is most common among rare inherited coagulation disorders [2]. The prevalence of Factor VII deficiency is 1:500,000 globally [2,3]. The prevalence is greater in populations with consanguineous marriage, as is common in Bedouin society. Factor VII deficiency manifestations display a wide spectrum of clinical

of factor VII and its low concentration in plasma increase the risk for volume overload, as well as the risk of transfusion reactions and infections.

In this retrospective study, we compared clinical and laboratory findings of patients with factor VII deficiency from different ethnic populations (Jewish and Bedouin) who were living in southern Israel and were diagnosed and treated at Soroka University Medical Center.

**PATIENTS AND METHODS**

We included all patients diagnosed with factor VII deficiency on laboratory tests who were treated at Soroka Medical Center, a tertiary hospital in the Negev region of Israel from 2005 to 2015. Patients were not included if they presented with a combined bleeding disorder, if the deficiency was attributable to a temporary condition (e.g., sepsis, extensive burns), or if data were missing. Patients who were lost to follow-up or who were originally diagnosed at a different hospital and then transferred to our facility were not included.

We used the European Network of Rare Bleeding Disorders graded severity of bleeding for the purpose of clinical trials as follows [9]:

- Asymptomatic: no bleeding
- Grade I: bleeding following trauma or antithrombotic therapy
- Grade II: spontaneous minor bleeding (e.g., epistaxis, menorrhagia)
- Grade III: spontaneous major bleeding (e.g., central nervous system, gastrointestinal)

We retrospectively reviewed all patients at Soroka Medical Center who were classified as having rare coagulation disorders (ICD9: 2863) between January 2005 and December 2015. Those patients with factor VII deficiency (activity under 60%) were identified.

For all patients, factor VII activity assay was performed with the Instrumentation Laboratory ACL TOP using prothrombin time method and a factor-deficient substrate. With this method, patient plasma is combined and incubated with factor VII-deficient substrate (normal plasma depleted of factor VII by immunoabsorption). After a specified incubation time, a prothrombin time reagent is added to trigger the coagulation process in the mixture. In addition, medical records of factors XIII, VIII, and II examination were reviewed.

The data were coded and stored using Microsoft Excel (97-2003 Workbook) software (Microsoft Corp, Richmond, CA, USA) and then transformed. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 23 (SPSS, IBM Corp, Armonk, NY, USA). First, descriptive statistics demonstrating the means,

distribution, and variance of relevant variables were presented [Table 1]. The two population groups were then compared using Pearson’s chi-square test for categorical variables, Fisher’s exact test for binary variables, and Student’s *t*-test and Mann-Whitney tests (*P* < 0.05) for continuous variables.

**RESULTS**

From our database, we identified the medical records of 793 patients with coagulation deficiencies. These diagnoses included deficiencies in factors VII, II, III, XI, XII, and XIII, as well as proteins C and S. From this group, we enrolled only patients with factor VII deficiency with factor levels under 60% and according to the characteristics we identified. A total of 78 patients met the criteria and were enrolled in our study. Of these, 60 were Jewish (76.9%) and 18 (23.1%) were Bedouin. The age at diagnosis varied from very early infancy to 40 years. The follow-up period varied from a few days after diagnosis and death (in three children who died soon after diagnosis) to many years.

Table 1 summarizes and compares the background data of both groups. In both groups, the majority of patients were females.

The main reason leading to diagnosis in both groups was an incidental laboratory finding: 31 Jewish patients (51.7%) and 8 Bedouin patients (44.4%). Most patients in both groups were asymptomatic: 41 Jewish (68.3%) and 12 Bedouin (66.7%). Only

**Table 1.** Background data for 78 enrolled patients

| Characteristic                              | Jewish<br>n=60<br>(76.9%)          | Bedouin<br>n=18<br>(23.1%) | P<br>value |        |
|---------------------------------------------|------------------------------------|----------------------------|------------|--------|
| Gender, men                                 | 27 (45%)                           | 8 (44.4%)                  | 0.967      |        |
| Gender, woman                               | 33 (55%)                           | 10 (55.6%)                 |            |        |
| Age at diagnosis, years                     | 25.6 ± 22.9                        | 9 ± 10.3                   | < 0.001    |        |
| Reason for diagnosis                        | Bleeding incident                  | 3 (5%)                     | 4 (22.2%)  | 0.185  |
|                                             | Incidental laboratory findings     | 31 (51.7%)                 | 8 (44.4%)  |        |
|                                             | Diagnosed family member            | 3 (5%)                     | 1 (5.6%)   |        |
|                                             | Bleeding after a medical procedure | 4 (6.7%)                   | 2 (11.1%)  |        |
|                                             | Unknown                            | 19 (31.7%)                 | 3 (16.7%)  |        |
| Severity of bleeding*                       | Asymptomatic                       | 41 (68.3%)                 | 12 (66.7%) | 0.0159 |
|                                             | Grade I                            | 8 (13.3%)                  | 1 (5.6%)   |        |
|                                             | Grade II                           | 11 (18.3%)                 | 1 (5.6%)   |        |
|                                             | Grade III                          | 0 (0%)                     | 3 (16.7%)  |        |
| Severity of factor VII deficiency in plasma | Mild deficiency (level > 30%)      | 20 (33.3%)                 | 7 (38.9%)  | 0.8365 |
|                                             | Moderate deficiency (level 11–30%) | 19 (31.7%)                 | 5 (27.8%)  |        |
|                                             | Severe deficiency (level < 10%)    | 21 (35%)                   | 5 (27.8%)  |        |
| Known asymptomatic ill relatives            | 8 (13.3%)                          | 1 (5.6%)                   | 0.365      |        |

\*We did not look at the severity of bleeding at a specific time point (i.e., diagnosis, for example), but if the patient at any time during follow-up had a bleeding incident, it was graded according to the European Network of Rare Bleeding Disorders

nine patients had relatives who were asymptomatic carriers of a factor VII mutation: 8 Jewish (13.35%) and 1 Bedouin (5.6%).

Patients who present with factor VII deficiency tend to experience bleeding, either at diagnosis or later in life. Thus, we did not look at the severity of bleeding at a specific time point (i.e., diagnosis for example), but if a patient at any time during follow-up had a bleeding incident we graded them according to the European Network of Rare Bleeding Disorders.

Among Bedouin patients, the severity of bleeding was higher than that recorded in Jewish patients ( $P = 0.0159$ ).

Table 2 shows the management and outcome in both groups. Six Jewish (10%) and five Bedouin (27.8%) patients had complications ( $P = 0.057$ ), and 35 Jewish (59.3%) and 7 Bedouin (38.9%) patients required peri-procedural prophylaxis. Five Jewish (8.3%) and four Bedouin (22.2%) patients required treatment while bleeding.

A considerable difference was noted between the two groups with regard to preventive treatment: 0 Jewish (0%) and 3 Bedouin (16.7%) ( $P = 0.011$ ); and fatality: 0 (0%) Jewish and 3 (16.7%) Bedouin ( $P = 0.0107$ ).

## DISCUSSION

This study comprised 78 patients diagnosed with factor VII deficiency who were treated at Soroka University Medical Center. This tertiary center provides healthcare and laboratory services for approximately 1 million people [14,15]. The known worldwide prevalence of factor VII deficiency is 1:500,000 [2,8]. We found a much higher prevalence in our study of for factor VII deficiency, (activity under 60%) 1:13,000, and for severe factor VII deficiency (activity 10% and under) 1:40,000. We do not know the reason for this high prevalence of factor VII deficiency, but we suggest that the screening of the population treated in our center was more comprehensive and exact

because the entire population of southern Israel is treated in our medical center and therefore fewer cases were missed. Another explanation could be related to the higher reported prevalence of the disease in countries or regions with more homogenous populations where consanguineous marriages are more common [13]. In our region, some populations are homogenous, such as Jews of North African descent, Ashkenazi Jews, and Bedouin. The Bedouin population has a high prevalence of consanguineous marriage. Specifically, in our study all the patients who died in infancy were born to Bedouin parents who were related.

This study aimed to compare the clinical and laboratory findings in patients with factor VII deficiency in two ethnic populations: Bedouin and Jewish. The main finding of this study was that Bedouin patients have more complications, a greater need for preventive treatment, and higher fatality rates. This result is consistent with our findings that Bedouin patients have higher severity of bleeding, which may be explained by consanguineous marriage in the Bedouin community and the homozygous condition causing a more severe illness. We did not find a specific family or tribe, Jewish or Bedouin, with a large number of diagnosed patients.

## LIMITATIONS

We did not perform a multivariable regression due to the small number of patients, and therefore there might be other variables influencing the results.

The number of enrolled patients was small, making a multivariable regression impossible. As for many studies that use retrospective data, ours is also affected with missing data due to the retrospective nature of our work. When looking at the prevalence of factor VII deficiency in our study, the numbers are most likely an underestimation due to the fact that most of the diagnosed patients with factor VII deficiency will be diagnosed after moderate to severe bleeding, and/or they are relatives of patients diagnosed with this deficiency. Thus, we can look at our study as representing only the lower range of this disorder and most likely it is considerably more prevalent, which necessitates further research to assess the real prevalence of this disease in the Negev population.

We retrospectively extracted our data from pre-existing medical files and therefore some data may be missing. However, our hematology laboratory incorporates information from all southern Israel healthcare providers, making the database comprehensive and as accurate as possible.

## CONCLUSIONS

The prevalence of factor VII deficiency in southern Israel is higher than reported in the literature and should be further investigated in terms of etiology and characteristics of the deficiency. The Bedouin community has higher complication and fatality rates as well as a greater need for preventive treatment.

**Table 2.** Management and outcome

| Characteristic                       | Jewish<br>n=60<br>(76.9%) | Bedouin<br>n=18<br>(23.1%) | P<br>value |
|--------------------------------------|---------------------------|----------------------------|------------|
| Major bleeding during follow-up*     | 6 (10%)                   | 5 (27.8%)                  | 0.057      |
| Received prophylactic treatment      | No                        | 60 (100%)                  | 0.011      |
|                                      | Recombinant factor VII    | 0 (0%)                     |            |
| Received peri-procedural prophylaxis | No treatment needed       | 24 (40%)                   | 0.128      |
|                                      | Treatment needed          | 35 (58.3%)                 |            |
| Received treatment due to bleeding   | No treatment needed       | 55 (91.7%)                 | 0.106      |
|                                      | Treatment needed          | 5 (8.3%)                   |            |
| Death                                | 0 (0%)                    | 3 (16.7%)**                | 0.0107     |

\*Major bleeding was defined as one of the following: intra-cranial bleeding, bleeding event required hospitalization in an intensive care unit, bleeding event requiring the administration of blood products, bleeding event requiring surgical intervention

\*\*All of the patients who died in infancy were born to Bedouin parents who were relatives, all deaths were soon after delivery

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**Capsule**

**AIRE and autoreactivity**

Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy is a condition caused by mutations in the gene encoding the autoimmune regulator (AIRE) and is associated with central T cell tolerance defects and circulating autoantibodies. **Sng** et al. observed that the altered development of T cells seen in AIRE deficiency is associated with a greater frequency of autoreactive B cells in the

periphery. This defect in B cell tolerance to self-antigens is linked to reduced numbers of certain regulatory T cells. This T cell defect may allow the selection and expansion of B cells that are autoreactive to peripheral self-antigens, thus leading to autoantibody production.

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**Capsule**

**Prioritization of cancer therapeutic targets using CRISPR–Cas9 screens**

Functional genomics approaches can overcome limitations such as the lack of identification of robust targets and poor clinical efficacy, which hamper cancer drug development. **Behan** and colleagues performed genome-scale CRISPR–Cas9 screens in 324 human cancer cell lines from 30 cancer types and developed a data-driven framework to prioritize candidates for cancer therapeutics. The authors integrated cell fitness effects with genomic biomarkers and target tractability for drug development to systematically prioritize new targets in defined tissues and genotypes. They verified one of the most promising

dependencies, the Werner syndrome ATP-dependent helicase, as a synthetic lethal target in tumors from multiple cancer types with microsatellite instability. This analysis provides a resource of cancer dependencies, generates a framework to prioritize cancer drug targets and suggests specific new targets. The principles described in this study can inform the initial stages of drug development by contributing to a new, diverse and more effective portfolio of cancer drug targets.

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**“I do not know anyone who has gotten to the top without hard work. That is the recipe. It will not always get you to the top, but it will get you pretty near”**

Margaret Thatcher (1925–2013), stateswoman who served as Prime Minister of the United Kingdom from 1979 to 1990 and leader of the Conservative Party from 1975 to 1990