Idiopathic purpura fulminans with anti-PS antibodies in children: a multicenter case series and systematic review

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Abstract:
Idiopathic purpura fulminans (IPF) is a rare but severe pro-thrombotic coagulation disorder that can occur after chickenpox or HHV6 infection. IPF leads to an autoantibody-mediated decrease in the protein S plasma concentration. We conducted a retrospective multicenter study involving IPF patients from 13 French pediatric centers and a systematic review of literature-published cases. Eighteen patients were included in our case series, and thirty-four as literature review cases. The median age was 4.9 years and the diagnostic delay after the first signs of viral infection was 7 days. The lower limbs were involved in 49 (94%) patients with typical lesions. A recent history of VZV or HHV6 infection was present in 41 (78%) and 7 (14%) of cases, respectively. Most of the patients received heparin (n=51, 98%) and fresh frozen plasma transfusions (n=41, 79%); other treatment options were immunoglobulin infusion, platelet transfusion, corticosteroid therapy, plasmapheresis, and coagulation regulator concentrate infusion. The antithrombin level and platelet count at diagnosis appeared to be associated with severe complications. Given the rarity of this disease, the creation of a prospective international registry is required to consolidate these findings.

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Idiopathic purpura fulminans associated with anti-PS antibodies in children: a multicenter case series and systematic review

Short title: Idiopathic purpura fulminans: a French study

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KEY POINTS

Idiopathic purpura fulminans has a typical clinical presentation with involvement of the lower limbs corresponding to vascular territories.

The antithrombin level and platelet count at diagnosis appeared to be associated with severe complications in IPF.

ABSTRACT:

Idiopathic purpura fulminans (IPF) is a rare but severe pro-thrombotic coagulation disorder that can occur after chickenpox or HHV6 infection. IPF leads to an autoantibody-mediated decrease in the protein S plasma concentration. We conducted a retrospective multicenter study involving IPF patients from 13 French pediatric centers and a systematic review of literature-published cases. Eighteen patients were included in our case series, and thirty-four as literature review cases. The median age was 4.9 years and the diagnostic delay after the first signs of viral infection was 7 days. The lower limbs were involved in 49 (94%) patients with typical lesions. A recent history of VZV or HHV6 infection was present in 41 (78%) and 7 (14%) of cases, respectively. Most of the patients received heparin (n=51, 98%) and fresh frozen plasma transfusions (n=41, 79%); other treatment options were immunoglobulin infusion, platelet transfusion, corticosteroid therapy, plasmapheresis, and coagulation regulator concentrate infusion. The antithrombin level and platelet count at diagnosis appeared to be associated with severe complications.
Given the rarity of this disease, the creation of a prospective international registry is required to consolidate these findings.
INTRODUCTION

Idiopathic purpura fulminans (IPF) is a rare syndrome, first described by D’Angelo and Levin.¹² Unlike acute infectious purpura fulminans, which is due to an active and severe bacterial infection, IPF is related to an acquired protein S (PS) deficiency secondary to viral infection by varicella-zoster virus (VZV) or human herpesvirus 6 (HHV6) that promotes the production of PS autoantibodies. The most likely mechanism is cross-reactivity against the virus and PS via molecular mimicry.³ IPF has been mainly described in case reports or small case series.²⁻⁴ Although IPF can be complicated by extensive skin necrosis and limb amputation, the treatment is not well defined.

Our study sought to describe patient characteristics, treatments, and outcomes of IPF by pooling the results of this French multicenter case series along with patients described in the literature. Our secondary objective was aimed at the identification of prognostic factors. Lastly, we propose a decision tree for diagnostic management and leads for the treatment.

METHODS

Case series

This was a multicenter study at 13 French pediatric academic centers (Montpellier, Marseille, Reims, Grenoble, Poitiers, Paris-Necker, Paris-Robert-Debré, Nantes, Nice, Nancy, Tours, Strasbourg, and Lyon). The main French centers of intensive pediatric hematology were contacted to participate in this retrospective study. The inclusion criteria comprised the presence of clinical IPF with a low level of PS and/or a history of viral infection in the 15 days prior to IPF in children under 15 years of age. The exclusion criteria comprised, previously published cases, other causes of infectious purpura fulminans (pneumococcus, meningococcus, etc.), severe congenital protein C and S deficiency, cancer, and hematological malignancies. The data were collected via a survey as well as the information available in the patients’ files. Data including the clinical and the biological characteristics of patients at admission, treatments, and outcomes were collected. The time to diagnosis (TTD) was calculated from the first signs of viral infection to the diagnosis of IPF. The extent of lesions was evaluated from clinical descriptions and photographs. The PS level is provided according to the assay method used: activity, free antigen, or total antigen, which are expressed as a percentage. Antithrombin (AT) and protein C (PC) are expressed as the percentage of normal activity, the fibrinogen level is expressed in g/L, and the platelet count in G/L when available on admission. D-dimer levels were considered to be increased if they exceeded the laboratory standard. The diagnosis of viral infection was clinical for chickenpox with or without biological confirmation of varicella-zoster virus (VZV), and biological by serology or polymerase chain reaction (PCR) for human herpesvirus 6 (HHV6).
The study was approved by the institutional review board of Montpellier University Hospital on behalf of all participating centers and was conducted in accordance with the provisions of the Declaration of Helsinki.

**Literature review cases**

In the absence of a case series with sufficient clinical and biological data on this pathology, we decided to pool clinical cases from the literature despite the limitations of this methodology. Our results consider the limitation that the previously published cases may not represent all cases at those individual institutions and may not be fully representative of the study population. The MEDLINE (1946 to 1 July 2019) database was used with the following keywords: “idiopathic purpura fulminans,” “acquired protein S deficiency,” and “anti-protein S antibodies.” Our search was limited to children. All articles that met the inclusion criteria and that presented sufficient data were included. The same data were collected as in retrospective case series.

**Statistical analysis**

The continuous variables are presented as medians with the minimum and maximum values, the dichotomous relative to the total number. For each data set, we show the number of missing data, when this was the case.

Extensive necrosis leading to distal amputation or skin necrosis were classified as severe thrombotic complications. To determine factors associated with the occurrence of severe complications, we reported the distribution of the median of each factor according to the patients’ outcomes (severe thrombotic complications). The median distributions were compared using Student’s $t$-test if they had a normal distribution, while Mann-Whitney tests were used otherwise. We used multiple univariate logistic regression models with the sociodemographic and the biological factors at the time of diagnosis. The regression models for the biological factors are inverted to present the effect when they decreased. We then constructed a multivariate logistic regression model using a stepwise selection with variables with a $p$-value < 0.2 in the univariate analyses as well as the patient’s age.

**RESULTS**

**Data extraction**

Between the 1st of January 1989 and the 31st of December 2018, we included 18 children from 13 French pediatric units (n=6, Montpellier; n=1, Marseille, Reims, Grenoble, Poitiers, Paris-Necker, Paris-Robert-Debré, Nantes, Nice, Nancy, Tours, Strasbourg, and Lyon) in the case series. In the literature review, we found 27 relevant articles published between 1992 and 2019. We excluded two of these articles due to insufficient data, while in the remaining 25 we excluded four cases from two case series, one for lack of data and three that did not meet the inclusion criteria. Ultimately, we retained 34 cases.
in 25 articles as literature review cases\textsuperscript{1-3,5-26}. The data presented below are the pooled results of 52 cases from both the case series and the literature review unless indicated otherwise. The case series results, and the literature review results are presented separately in Table 1.

Characteristics at admission

The median age at diagnosis was 4.9 years (1.5-11) and the sex ratio (M/F) = 0.52. The TTD was 7 days (2-17). The clinical presentation was an ecchymotic or necrotic purpura of a lower limb (n=49; 94%), the calves only (n=13; 25%), an upper limb (n=7; 13%), the torso (n=11; 21%), or the genitalia (n=4; 8%). Several patients presented with identical vascular territories such as ‘sock-like’ lesions of the calves and/or necrosis of the anterolateral side of the thigh (Figure 1).

A diagnosis of viral infection was confirmed for 45 patients (86%): chickenpox (n=41; 78%) or HHV6 (n=4; 8%). PS deficiency was confirmed in all the patients. The median PS activity level was 4% (range 1-28). The median free PS antigen level was 1% (range 1-16) and the median total PS antigen level was 5% (range 1-62). The presence of anti-PS antibodies was confirmed in 30 patients (58%). At admission, the median AT activity level was 85% (range 45-130), the median PC activity level was 49.5% (range 14-131), the median fibrinogen level was 0.88 g/L (range 0.1-3.4), and the median platelet count was 150 G/L (range 10-302). D-dimer levels were tested in 36/52 cases (69%), and they increased in 30/36 cases (83%).

Treatment and outcomes

The treatments included intravenous (IV) heparin (n=51; 98%), IV fresh frozen plasma (FFP) (n=41; 79%), IV polyvalent immunoglobulins (PIg) (n=20; 38%), IV corticosteroids (n=16; 31%), plasmapheresis (n=13; 25%), and IV coagulation inhibitor concentrates (AT or activated PC) (n=12; 23%).

The PS levels normalized in all the patients, albeit with variable time frames. The PS levels started to increase at 10 days (range: 2-49), with a normalization median delay of 60 days (range: 6-120). There were no deaths, although 25 patients (47%) had serious thrombotic complications including distal amputation (n=14; 27%) or skin necrosis with grafting (n=15; 29%) (four patients required both); 17 patients (33%) developed venous thromboembolism and two patients had a hemorrhage, one subarachnoid and one pulmonary alveolar hemorrhage.

We analyzed the relationship between several factors and the occurrence of severe complications in the overall cohort. At the time of diagnosis, the median AT activity level and the median platelet count were significantly lower in patients with severe complications, at 79% vs. 101%, respectively (P < 0.001) and 51.5 G/l vs. 188.5 G/L (P < 0.001), respectively. Univariate analyses confirmed the results, with odds ratios (ORs) of 1.08 [95% CI:1.03-1.14, P=0.003] for the median AT activity level and 1.02 [95% CI:1.01-1.02], P=0.001] for the median platelet count. In multivariate analysis, a correlation was found between severe complications and the median AT activity level, with an OR of 1.07 [95% CI:1.01-1.14,
and the median platelet count, with an OR of 1.01 [95% CI:1.00-1.02, \( P=0.04 \)]. All the results are presented in Figure 2 and Table 2.

**Decision tree for acute diagnostic and management**

We propose simple diagnostic criteria to help in the diagnosis.

**When to suspect idiopathic purpura fulminans?**

IPF is a serious condition that requires urgent management. The most relevant disease history data appears to be the existence of a VZV or HHV6 infection within 15 days before the purpura. On clinical examination, most patients (94%) had lower limb involvement, with typical lesions. IPF being very rare, it is necessary to eliminate the most frequent causes of purpura fulminans such as bacterial infections, which tend to present as states of severe sepsis or even septic shock with elevation of inflammatory markers such as C-reactive protein and procalcitonin, and they can be accompanied by meningeal irritation.

**How to confirm the diagnosis and start treatment quickly?**

The essential criteria for distinguishing purpura fulminans from other forms of purpura and coagulopathy is the presence of a protein S deficiency. Once the coagulation test has been performed, fresh plasma infusion and heparin therapy are the most widely used treatments. As the main risk is thrombotic complication, they can be started immediately in the absence of hemorrhagic signs.

**How to treat once the diagnosis is confirmed?**

Plasmapheresis and immunoglobulin infusions appear to be the two most effective treatments against the protein S inhibitor. It seems relevant, therefore, to administer them as soon as possible. Naturally, the continuation of an anticoagulant treatment remains essential, and the addition of antithrombin concentrate can be considered in case of deficiency.

We have summarized these proposals in Figure 3.

**DISCUSSION**

IPF is a rare disease that affects young children, with potentially severe sequelae such as distal amputations and extensive skin necrosis. The study of our case series confirms the natural history described in the literature. IPF starts 7 days after a VZV or HHV6 infection, leading to thrombotic complications that mainly affect the lower limbs. Anti-PS autoantibodies were found in more than half of the patients, thus suggesting the autoimmune origin of the disease linked with an infectious antigenic stimulus\(^2\). In our series, as in the literature, the autoantibodies appear to fully disappear within a few weeks, irrespective of the treatment used. Two studies have reported an asymptomatic decrease in the level of protein S in the context of infection by VZV, but without association to antibodies or thrombotic
The prevalence of anti-protein S antibodies is not known, nor are the factors that can favor progression to this acute and severe form of thrombophilia, as chickenpox and HHV6 infections are extremely common and IPF the exception.

The clinical lesions revealed a degree of similarity between patients, as the anatomical locations of the necrosis appeared to overlap with the anatomical vascular territories, such as perforating branches of the fibular artery, the tibial anterior artery, and the deep femoral artery. This suggests a complete thrombotic obstruction of the corresponding perforasome without replacement by adjacent areas. These anatomical data are consistent with the presence of targeted thrombosis in the distal limb circulation.

The biology at diagnosis reflected either a normal condition or signs of consumption (lowering of fibrinogen and platelets, elevation of D-dimers), which may be compatible with a diagnosis of DIC. A severe decrease in the level of protein S in most patients allows differentiation from conventional DIC. Protein S assays should, therefore, be performed promptly in case of any suspicion of IPF.

Most of the clinical cases described a rapid progression to severe thrombotic complications. Hence, IPF treatment must be effective to prevent the occurrence of thrombosis and to eliminate the antibody. In the literature, heparin anticoagulation and FFP infusion are the most used treatments, while the effectiveness of immunoglobulin infusions and plasmapheresis to decrease the inhibitor has been suggested in several case reports. In our study, the AT level and platelet count at diagnosis appeared to be associated with severe complications. During conventional DIC, the AT level decreases by consumption at an early phase of the DIC, and it can predict the outcome. It raises the question of AT concentrate infusions in patients with decreased AT activity levels at diagnosis, as proposed for DIC.

To date, there are no targeted recommendations for the diagnostic and therapeutic management of IPF in the context of protein S antibodies. In Figure 3, we propose straightforward criteria for the diagnosis and management of these patients in a fast and effective way to as best as possible limit the sequelae related to the severe thrombotic complications. The key points of the diagnostic management are the clinical history, with the occurrence of a recent varicella infection or elements in favor of a primary HHV6 infection, and the presence of purpura lesions of the lower limbs with involvement in the vascular territory. The absence of signs of shock, more commonly found in DIC, is also an important factor, as septic signs, and systemic inflammation (elevated C-reactive protein and procalcitonin) are observed in acute infectious purpura fulminans. Conventional coagulation tests do not allow a clear-cut decision to be made, and only an emergency determination of protein S allows confirmation of the diagnosis. Detection of an antibody takes too much time; protein S deficiency is sufficient to make an emergency diagnosis. As soon as the diagnosis is suspected or confirmed, treatment with heparin anticoagulation and FFP infusion should be started without delay. Plasmapheresis and Ig infusions can be administered in a timely manner.
A major limitation of our study is the small number of patients. The literature review cases make it possible to increase the number of patients, but it adds a selection bias since only the most significant cases are published. The similarity of the results between our retrospective case series and the literature review cases is reassuring in this regard.

Given the rarity of this disease, a prospective international registry might be an appropriate solution to progress the understanding and management of IPFs.
Data sharing statement:

For data sharing, contact the corresponding author: a-theron@chu-montpellier.fr.

Author contributions and disclosures:

Theron A designed the research, collected, and analyzed data, and wrote the paper. Dautremey O designed the research and collected data. Boissier E designed the research. Zerroukhi A collected data. Baleine J wrote the paper. Moulis L analyzed the data. Rodière M collected data. Schved JF wrote the paper. Duraes M wrote the paper. Kanouni T wrote the paper. Jeziorski E designed the research, analyzed the data, and wrote the paper. Biron-Andreani C designed the research, analyzed the data, and wrote the paper.

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Figure 1. Schematic depiction of typical lower limb lesions observed in many cases, with corresponding pictures of affected areas.

Figure 2: Box plot showing the age distribution, fibrinogen level, platelet count, antithrombin level and protein C activity at the time of diagnosis according to patient outcome (with or without amputation and/or skin graft). The box represents the interquartile (25th to 75th percentiles) range. The horizontal line in the box represents the median. The whiskers represent the maximum and minimum values. A. for case series patients. B. For all patients (cases series and literatures review cases). The p-value was estimated using Mann-Whitney non-parametric U test or Student’s t-test. * P < 0.05; **P < 0.01; *** P < 0.001.

Figure 3. Proposed Algorithm for diagnostic and treatment of idiopathic fulminans purpura.

Table 1. Characteristics of patients, clinical presentation, type of virus, biology at diagnosis, treatment, and outcomes. *Antithrombin and activate protein C. VZV: Varicella-zoster virus, HHV6: human herpesvirus 6.

| Patient characteristics | Case series (n=18) | Literature review cases (n=34) | Pooled data (n=52) | Missing Data n(%) |
|-------------------------|-------------------|-------------------------------|-------------------|-------------------|
| Median age (range), years | 4.4 (1.5-6) | 5.2 (1.8-11) | 4.9 (1.5-11) | - |
| Male gender, N (%) | 7 (39) | 20 (59) | 27 (52) | - |

| Clinical presentation | | | |
|-----------------------|-----------------|-----------------|-----------------|
| Median time to diagnosis (range), days | 6 (2-17) | 8 (5-15) | 7 (2-17) | - |
| Lower limb, N (%) | 16 (89) | 33 (97) | 49 (94) | - |
| Calves only, N (%) | 3 (17) | 10 (29) | 13 (25) | - |
| Extended leg, N (%) | 13 (72) | 23 (68) | 36 (69) | - |
| Upper limb, N (%) | 2 (11) | 5 (14) | 7 (13) | - |
|                  | Genitalia, N (%) | Torso, N (%) | Virus | Biology at diagnosis | Treatments |
|------------------|------------------|--------------|-------|---------------------|------------|
|                  | 1 (5.6)          | 3 (9)        | 4 (8) | -                   | -          |
|                  | 3 (17)           | 8 (23)       | 11 (21) | -                   | -          |
| **Genitalia, N (%)** | 1 (5.6)          | 3 (9)        | 4 (8) | -                   | -          |
|                  | 3 (17)           | 8 (23)       | 11 (21) | -                   | -          |
| **Virus**        |                  |              |       |                     |            |
| HHV6, N (%)      | 3 (17)           | 1 (3)        | 4 (8) | -                   | -          |
| VZV, N (%)       | 11 (61)          | 30 (86)      | 41 (78) | -                   | -          |
| Unknown, N (%)   | 4 (22)           | 4 (11)       | 7 (14) | -                   | -          |
| **Biology at diagnosis** |                |              |       |                     |            |
| Median protein S activity (range), % | 5 (1-28)        | 2.5 (1-25)   | 4 (1-28) | 24 (52)         |            |
| Median protein S free antigen (range), % | 6 (1-16)        | 1 (1-9)      | 1 (1-16) | 24 (46)         |            |
| Median protein S total antigen (range), % | 4.5 (1-32)      | 5.5 (1-62)   | 5 (1-62) | 22 (42)         |            |
| Anti-protein S antibody, N (%) | 13 (72)         | 17 (50)      | 30 (58) | -                   |            |
| Median protein C activity (range), % | 43 (14-131)     | 54 (14-100)  | 49.5 (14-131) | 4 (8)        |            |
| Median antithrombin level (range), % | 85 (45-130)     | 86 (48-115)  | 85 (45-130) | 11 (21)       |            |
| Median fibrinogen level (range), g/l | 1.85 (0.35-3.4) | 0.5 (0.1-2.38) | 0.88 (0.1-3.4) | 10 (19)     |            |
| Median platelet count (range), G/l | 65 (10-250)     | 166 (14-302) | 150 (10-302) | 8 (15)        |            |
| D-Dimer increase, N (%) | 14 (78)         | 16/18 (89)   | 30/36 (83) | 17 (33)        |            |
| **Treatments**   |                  |              |       |                     |            |
| Heparin, N (%)   | 18 (100)         | 33 (97)      | 51 (98) | -                   | -          |
| Corticosteroid, N (%) | 3 (17)         | 13 (37)      | 16 (31) | -                   | -          |
| Fresh frozen plasma, N (%) | 13 (72)         | 29 (83)      | 41 (79) | -                   | -          |
| Polyvalent immunoglobulin, N (%) | 8 (44)         | 11 (31)      | 20 (38) | -                   | -          |
| Outcome                                | OR   | 95% CI    | P value | aOR | 95% CI    | P value |
|----------------------------------------|------|-----------|---------|-----|-----------|---------|
| Gender: Female                         | 0.60 | 0.12-3.00 | 0.53    | -   | -         | -       |
| Age*                                   |      |           |         |     |           |         |
| < 4.5 years old                        | 2.02 | 0.54-7.49 | 0.49    | -   | -         | -       |
| 4.5-6 years old                        | 1.83 | 0.43-7.77 | 0.69    | -   | -         | -       |
| > 6 years old                          | REF  | REF       | REF     | -   | -         | -       |
| Antithombin†                           | 1.08 | 1.03-1.14 | 0.003   | 1.07| 1.01-1.14 | 0.03    |
| Fibrinogen†                            | 1.08 | 0.55-2.13 | 0.82    | 1.01| 1.00-1.02 | 0.04    |
| Platelets†                             | 1.02 | 1.01-1.02 | 0.001   | -   | -         | -       |
| Protein C †                            | 1.02 | 1.00-1.05 | 0.08    | -   | -         | -       |

Table 2. Results of univariate and multivariate logistic regression for the risk of severe thrombotic complications (amputation, skin necrosis with grafting). *Age did not have a normal distribution in our series; we considered three age brackets according to the distribution of the patients. †Regression models for biological factors are inverted to present the effect when they decreased.
Figure 2

A

- Age (month)
- Fibrinogen (g/L)
- Platelet count (G/L)
- Antithrombin (%)
- Protein C activity (%)

B

- Age (month)
- Fibrinogen (g/L)
- Platelet count (G/L)
- Antithrombin (%)
- Protein C activity (%)

- Patient without amputation and/or skin graft
- Patient with amputation and/or skin graft
Figure 3

Suspected idiopathic fulminans purpura

- History of viral infection 15 days prior to purpura
- Typical lower limb lesions
- Absence of signs suggestive of meningococcemia (neurologic symptoms, septic shock, systemic inflammation)

Confirm diagnosis and prepare to treat

- Dosing of protein S
- Start plasma infusion and heparin if necrotic purpura
- Prepare for plasmapheresis or polyvalent immunoglobulin

Low level of protein S (< 30%)

- Start plasmapheresis
- If plasmapheresis is not available in the emergency unit, start infusion of polyvalent immunoglobulin
- Continue heparin therapy
- If AT activity is low consider antithrombin infusion