Clinical aspects and medico-legal implications of purpura fulminans in children

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Abstract: Purpura fulminans is a particular clinical entity of infectious or non-infectious etiology, which consists of an array of physio-pathological processes with rapid evolution towards intra-vascular disseminated coagulation (IDC) and multiple organ failure and death in most cases. Depending on illness evolution and timely hospital admission, death can occur in less than 24 hours, which carries medico-legal implications regarding the patient's death.

Purpura fulminans is frequently encountered in children, predominantly in the 0-1 years age group but also in the young adult. Currently, this condition has a declining incidence due to the introduction of meningococcal and pneumococcal vaccinations.

In this paper we propose to analyze cases of pediatric purpura fulminans of infectious etiology admitted in the pediatric clinic of the National Institute for Infectious Diseases "Prof. Dr. Matei Bals" Bucharest. In these cases, we have evaluated etiology as well as clinical evolutionary forms of purpura fulminans, as well as the timeline from admission to death.

Regarding etiology, most cases were meningococcemias; diagnosis was established on clinical criteria and confirmed through specific laboratory methods. There were situations when the patients presented themselves too late at the hospital and death took place within hours from admission. Mortality for pediatric purpura fulminans was 41.93 % out of which 76.92 % died in the first 24 hours from admission, these cases requiring necropsy because of its medico-legal implications. In all cases where a necropsy was performed, the pathology report confirmed the diagnosis of ICD with multiple-organ failure through purpura fulminans.

Infectious pediatric purpura fulminans is a severe condition with a high mortality, especially in the epidemiological conditions of Romania where vaccination coverage is low in general and pneumococcal and meningococcal vaccinations are optional.

Key Words: sepsis, mortality, child.

INTRODUCTION

Purpura fulminans (PF), initially described by Guelliot in 1884, is a life-threatening condition with a rapid evolution characterized by typical cutaneous lesions, intra-vascular disseminated coagulation, multiple organ failure and septic shock. The severe form of this illness is also known as Waterhouse Friderichsen syndrome which is generally associated with fulminant meningococcemia (caused by Neisseria meningitidis), but can also be caused by viruses such as cytomegalovirus, HIV, parvovirus B19, Epstein Barr virus and bacteria such as Staphylococcus aureus, Haemophilus influenza, Streptococcus pneumoniae, Pseudomonas aeruginosa, Escherichia coli, Mycobacterium tuberculosis and fungi, Histoplasma capsulat. Non-infectious causes consist of birth, pregnancy, idiopathic adrenal vein thrombosis, supra-renal metastasis, seizures, anti-convulsants, phlebographies, trauma, and surgery [1, 3].

Purpura fulminans is a major medical
emergency which can appear after an upper respiratory tract infection with a sudden onset: hyperthermia, headaches, irritability, digestive symptoms, and altered general state. Signs and symptoms can vary and often are unexpected and unpredictable. Clinical presentation can be grouped in three categories: infectious syndrome (fever, headache), purpuric syndrome (rapidly extending petechiae, ecchymoses, subcutaneous hematomas) and endotoxic shock (hypotension, tachycardia, oliguria and polynea). Even with aggressive therapy, death can take place in 24-36 hours. Upon onset, patients can show flank, epigastrium, abdominal pain, severe headache, malaise, vertigo, vomiting, and apathy. Subsequently hypotension, collapse, petechiae, mucocutaneous petechiae, which converge resulting in large purpuric areas (flowers of death). The rash is present in approximately 75% of patients and begins as a pinkish macular-papular rash, localized on the extremities. The petechiae can appear initially on the joints of the hand, ankle, in the axillas, and will extend to the entire surface of the body including the mucosae (epistaxis, hematuria, upper digestive bleeding, gum bleeding) [2, 10].

Regarding physio-pathology, multiple factors seem to be involved: ACTH, spasm and thrombosis of the supra-renal veins, limitation of venous drainage. The supra-renal glands have a rich arterial vascularization as opposed to venous vascularization which is limited to a single vein. In stressful situations, ACTH secretions rise, stimulating arterial flow, which exceeds the venous drainage, leading to hemorrhage. Furthermore, the spasm of the supra-renal vein triggered by circulating catecholamines released in stressful situations and the thrombosis triggered by circulating coagulopathies lead to venous stasis and hemorrhage. In fulminant meningococcemia, a key role is held by endotoxins, lipooligosaccharide (LOS). The concentration of endotoxins in the blood of patients with fulminant meningococcemia is 10 to 100 times greater than in patients with gram negative bacteremia. LOS stimulates monocytes, neutrophils, and endothelial cells, which release cytokines and inflammatory mediators. The activated endothelium expresses on its surface procoagulant molecules (adhesins) which trigger disturbances in the microcirculation. Building of fibrine deposits is favored by the procoagulant tendency (through activation of the tissue factor and the low level of C protein and antithrombin) and the antifibrinolytic tendency [1, 10].

Mortality by purpura fulminans is very high; coagulopathy occurs in 80-100% of cases, and persistent disabilities (amputations) are frequent is survivors. Studies carried out on multiple cases suggest that substituting protein C zymogen can significantly reduce the coagulopathy, amputation rate, and improve survival rates [6, 7].

OBJECTIVES

We have studied pediatric cases of purpura fulminans, in which we have analyzed clinical forms and evolution of Waterhouse Friedrichsen syndrome, mortality rates, as well as medico-legal implications (correlation between necropsy results and clinical/laboratory diagnosis).

MATERIAL AND METHOD

We have carried out a retrospective study over 10 years (2008-2017) on all cases of purpura fulminans in children admitted in the National Institute for Infectious Diseases “Prof Dr. Matei Bals” Bucharest. In all cases we have analyzed age, sex, time lapsed from admission to death. Diagnosis was established on clinical criteria (on the presence of purpura with a rapid evolution towards petechiae and cutaneous necrosis, IDC) and laboratory criteria (confirmation of coagulopathy, endotoxic shock, MSOF). Infectious etiology was identified through specific diagnostic methods: blood cultures, cultures and smears from cutaneous lesions, PCR.

RESULTS AND DISCUSSION

In the mentioned period we have registered 31 cases of purpura fulminans in children admitted in the Pediatric Department of the National Institute for Infectious Diseases "Prof Dr Matei Bals". The number of cases was variable, with an average of 3.1 cases per year (1-7 cases/year).

The mortality rate in analyzed cases was 41.93% (13/31). Death occurred in the first 24 hours from admission in 76.92% (10/13) of cases (Fig. 1). Necropsy was performed on 6 cases, 46.15% of all deaths. Concordance between established diagnosis and necropsy results was 100%.

Etiology in most cases, 66.6% (20/30), was unknown. All deaths that took place in less than 24 hours from admission were cases of purpura fulminans with unknown etiology.

In cases where etiology was established,
meningococcal purpura fulminans were predominant - 63.33% (7/11), followed by pneumococcal 27.27% (3/11), and a single case of Pseudomonas aeruginosa (Fig. 2). Out of all meningococcal cases, most were caused by Neisseria meningitidis group B – 57.17% (4/7), group C - 28.57%, and one case of group Y – 14.28%. The data we obtained is similar to that reported by other authors in similar studies [4-6, 8, 9].

In Figure 3 we can see that purpura fulminans in children was predominant in male patients (70.96%); deaths were more frequent in female patients (53.84%, 7/13), but without statistical significance.

Most cases were registered in the 0-1 and 1-4 years age groups, in equal proportions (41.93%). We can observe that the majority of cases were in the 0-4 years age group (83.86%), data which corresponds with that of other authors in specialty literature [9].

Deaths were more frequent in the 0-1 and 1-4 years age groups, each accounting for 38.46%, totalling to a mortality rate of 76.92% in children under the age of 4 (Fig. 4). 80% (8/10) of patients who died in the first 24 hours were aged 1-4 years; the other 2 cases belonged in the 4-7 and 7-14 years age groups.

Autopsy was performed in 5 cases, 3 males and 2 females, aged 4-14 months (medium age 7.4 months). The death occurred soon after admission (3-36 hours, medium interval 13.3 h). In all these cases the autopsy was performed in order to confirm or complete the diagnosis; this was necessary due to the short period between the admission within the hospital and death. Also, in all the cases of death in children younger than one year old, the autopsy is necessary to exclude a possible malformation previously undetected.

All the patients had bilateral adrenal hemorrhagic necrosis (Fig. 5, A-F), prominent hyperemia and edema of the meninges and cerebral tissue, acute pulmonary congestion and edema (Fig. 5, J, K, L) and congestion of the liver, spleen and kidney (Fig. 5, M, N, O); three of them had acute leptomeningitis (Fig. 5, G, I, H - two of three being older with longer survival after admission); three patients had either hemorrhagic alveolitis (Fig. 5 K, L) or interstitial pneumonia (Fig. 5 I); all but one patient presented renal lesions consisting in either dystrophic lesions of the tubular cells (Fig. 5 M) - (two cases) or tubular epithelial cells necrosis (Fig. 5 N, O) (two cases) (see Table 1).

![Image](image1)

**Figure 2.** Distribution of cases of purpura fulminans in children according to etiology.

![Image](image2)

**Figure 3.** Sex distribution of cases of purpura fulminans.

![Image](image3)

**Figure 4.** Age distribution of purpura fulminans cases.

<table>
<thead>
<tr>
<th>Case no. 1</th>
<th>Case no. 2</th>
<th>Case no. 3</th>
<th>Case no. 4</th>
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**Table 1.** Main lesions identified during autopsy.
Figure 5. A-F - Adrenal gland: Adrenal gland enlarged and destroyed by massive acute hemorrhagic infarction with extensive cortical and medullary necrosis involving all the adrenal layers; marked hemosiderin dispositions. (Hematoxylin and eosin stain; magnification A, E x 100, B, C, D x 200, F x 400. G, I - Cerebral hemisphere with subarachnoidal space: Subarachnoidal space with vascular congestion, infiltrated with neutrophils and fibrin with perivascular margination. (Hematoxylin and eosin stain; magnification G x 200, I x 400). H - Cerebellum with subarachnoidal space: Subarachnoidal space with vascular congestion, infiltrated with neutrophils; preserved external granular layer of the cerebellum (Hematoxylin and eosin stain; magnification x 400). J - Lung: Lung with dilated capillaries within alveolar walls, hemosiderin deposits and interstitial pneumonia. (Hematoxylin and eosin stain, magnification x 200). K, L - Lung with large areas of alveolar hemorrhage. (Hematoxylin and eosin stain, magnification K x 200, L x 400). M - Kidney: congested interstitial capillaries and vacuolar degeneration of the epithelial tubular cells. (Hematoxylin and eosin stain; magnification x 400). N, O - Kidney: Kidney with hypereosinophilic cytoplasm of epithelial tubular cells devoid of nuclei, due to focal tubular necrosis (Hematoxylin and eosin stain, magnification N x 200, O x 400).
CONCLUSIONS

Purpura fulminans remains a severe condition with a high mortality rate, which carries medico-legal implications. Necropsy examinations in these patients is important for identifying the cause of death and settling its accordance with the clinical diagnosis. The role of the pathology examination is essential in these cases because the death of the patient takes place so fast despite complex treatment instituted within the intensive care unit.

Severe clinical forms associated with IDC and MSOF are frequently encountered in our study, these results being similar with those reported in specialty literature. Key roles are constituted by genetic factors, the timeliness of hospital admission as well as treatment institution. Still, even if diagnosis is established early and treatment is begun, mortality is very high. Mortality of pediatric purpura fulminans in our study was 41.93%; 79.92% of deaths occurred within 24 hours of admission. Necropsy results were in accordance with clinical and laboratory diagnosis. There were no cases with medico-legal implications or malpractice claims.

Reduction of purpura fulminans mortality can be accomplished through identification of genetic biological patterns associated with this condition as well as the introduction of mass meningococcal and pneumococcal vaccination.

Still, many etiological agents remain, for which no prophylactic measures can be taken.

Analyzing cases which died, we can observe that meningococcal purpura fulminans in children is more frequent in females and in the 0-4 years age group. All cases had a severe evolution with coagulopathy and multiple organ failure, death ultimately taking place through biological exhaustion and complications incompatible with life (cardiomyopathy, cerebral, pulmonary, suprenal hemorrhage, ICD).

The coroner’s office has an important role in the deaths of cases of purpura fulminans that require confirmation or identification of cause of death.

Conflict of interest. The authors declare that there is no conflict of interest.

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