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Waterhouse-Friederichsen syndrome in infants and children (Forensic case series)

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Abstract: Massive adrenal haemorrhage is an uncommon finding at autopsy, but patognomonic for Waterhouse-Friederichsen syndrome (WFS – described for the first time as clinical entity in 1911), ussually associated with fulminant meningococemia. Aim of our research was to analyze demographic, clinical and necroptic findings in cases of lethal WFS in infants and children (0 – 2 years). We conducted a retrospective study on forensic autopsy cases performed in Mures county between the years 2011 – 2015 by reviewing the necropsy protocols together with the clinical documentation and the reinterpretation of microscopic findings. During the period of five years, we found 133 cases of autopsies in the age group 0 – 2 years, among them in 5 cases (3.76%) WFS was revealed. Male gender prevailed (80%) and average annual incidence of fatal WFS was 5.88/100.000 relative to the population in our County of the same age group. A poor socioeconomic status was described in 4 out of 5 cases (80%). Time from onset of symptoms to death varied from 45 minutes to 8 hours. All children had earlier a form of respiratory infectious pathology. The typical rash of purple spots on the skin was described in four cases, while internal examination revealed cerebral edema and interstitial pneumonia also in four cases each. Adrenal necrosis was noticed in two cases and contrary to other reports in the literature, we found no myocardial infalmmatory involvement in any of our cases. Positive microbiological finding was noted in only one case (*Neisseria meningitidis*).

Key Words: Waterhouse-Friederichsen syndrome, adrenal haemorrhage, forensic autopsy.

INTRODUCTION

Waterhouse – Friderichsen Syndrome was for the first time described in 1911 by Rupert Waterhouse (an English physician) in an 8 month-old child. In 1918 Carl Friderichsen (a Danish pediatrician) described a similar case clinically characterized by stupor, cyanosis, vomiting, rapidly evolving with the emergence of a generalized purpura and bilateral massive adrenal hemorrhage at autopsy [1, 2].

This pathology constitutes a major emergency once the bleeding adrenal glands appeared, often accompanied by forms of sepsis with Meningococcus as the pathogen most frequently involved [1, 3, 4], in some cases Haemophilus influaenzae, Stapphylococcus aureus or Pneumococcus [4-6]. Other non – infectious etiologies have been also reported such as trauma, burns, treatment with anticoagulants, antifosolipidic syndrome, tumor metastasis, postsplenectomy etc. [7-11].

This clinical entity is more frequently seen in pediatric rather than the adult population and is associated with high morbidity and mortality [12-14]. Most cases have been reported in children aged 0-2 years, rapidly evolving towards death, usually within 24 hours of symptoms sonset [1,14].

Objectives of the study

We aimed to estimate the incidence of fatal WFS syndrome in infants and young children, to analyse the demographic, clinical and pathological features

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in cases of fatal WFS in infants and children (age 0-2 years) and to make anatomo-clinical correlations, with review of medical history. Macroscopic and microscopic systematization of pathological changes was a goal of our research as well.

MATERIAL AND METHOD

We made a retrospective descriptive casuistry study on autopsies performed at the Institute of Legal Medicine Tirgu Mures during the period 2011 - 2015, by extracting data from the necropsy protocols regarding deaths of infants and small children (0 – 2 years old) in which adrenal bleeding was noticed, followed by documenting clinical observation sheets of WFS cases when death occurred in the hospital and review of histopathologic slides.

RESULTS AND DISCUSSION

In the period studied (2011-2015) 3762 forensic autopsies have been performed in the Institute of Legal Medicine Tg. Mures, of which 1,800 (47.85%) cases of violent deaths and 1962 (52.75%) cases of nonviolent death. Deaths in the age group 0-2 years were 133 cases (3.54%) of which 22 violent deaths and 111 cases of nonviolent death. Gender ratio in this group revealed a slight predominance of males (59.4%). Among the total of autopsies in the age group 0-2 years, we found five cases of Waterhouse – Friderichsen syndrome (3.76%). WFS extrapolated incidence was 5.88/ year/ 100,000 population aged 0-2 years.

In the WFS group ages varied between 5 months and 2 years. WFS was more frequent in males (4 out of 5 cases) and in countryside areas with poor socio-economical status (4 out of 5 cases), similar to other sources [15]. Three of five cases were within the normal range of development and a weight deficit of grade II or III was present in 2 cases. All subjects had a history of a form of respiratory pathology [7, 9, 10], two of them were premature and 3 of 5 cases were not vaccinated according to the vaccination schedule. The time between onset of symptoms to the time of death ranged from 45 minutes the shortest – case 4) to roughly 8 hours (before being found dead the next morning - Case 3) (Table 1).

From the clinical perspective, the signs and symptoms may vary, most often unexpected and unpredictable. The onset is usually abrupt, with digestive and respiratory phenomena – pathologies commonly found in infants and small children. Symptoms are similar to that found in respiratory infections consisting of headache, cough, rhinorrhea, indisposition, symptoms found in 4 out of 5 cases (1, 2, 4 and 5) [3, 7, 16]. Vomiting, diarrhea, persistent smelly greenish faeces and abdominal pain were also common complaints. In all cases we noticed fever associated with digestive phenomena that have worsened dehydration and precipitated the development of low blood pressure with collapse tendency due to decreased extracellular volume by losses of mineralocorticoids leading to circulatory shock with tachycardia, polypnea, cyanotic extremities and lips associated with pale skin, moist, followed by purpuric syndrome (Table 2). Thus, with the development of generalized purpura, chances of survival are significantly reduced, the death rate rises to 90-95% [15,17].

These symptoms can be grouped into three categories: infectious syndrome (associating fever and headache), purpuric syndrome (with quickly generalized petechiae) and endotoxin shock with hypotension, tachycardia, oliguria and polypnea [14, 16, 18]. Sepsis can alter consciousness and cognition, compromising tissue perfusion due to fever, followed by psychomotor anxiety and seizures; tonico-clonic seizures were present in only one case of five, compared to generalized hypotonia that was more frequent. The temperature was moderately increased at the beginning of the disease, fever (38 – 39.1 grd. C) was noticed in three of the five cases [1]. The loss of mineralocorticoid due to adrenal hemorrhage, produces extracellular hypovolemia which reduces the circulatory volume and consequently lowers the blood pressure. Hypotension, tachycardia, and polipneea

Table 1. General data

General Data	Case 1	Case 2	Case 3	Case 4	Case 5
Gender	Female	Male	Male	Male	Male
Age	7 months	24 months	12 months	6 months	5 months
Environment of origin	rural	Rural	Urban	Rural	Rural
Socioeconomic status	Poor	Poor	Favorable	Poor	Poor
Nutritional status	6520 g, 70 cm	12000 g, 83 cm	8650 g,79 cm	4500g, 66 cm	3160 g, 50 cm
Vaccination status	unvaccinated			Unvaccinated	Unvaccinated
Place of death	Pediatrics	UPU-ATI	Home	UPU-SMURD	Pediatrics
Previous pathology	Acute angina Bronchitis	Acute Bronchitis	Hydronephrosis Vesicoureteral reflux Bronchitis	Acute angina	Pneumonia
Time to death	1 h 40 min	4 h 55 min	?(~ 8 h)	45 min	8 h

seen in 4 of 5 cases characteristic of this syndrome characterized toxic shock before death. Respiratory rate was increased sharply in all cases. In addition extremities presented cyanotic lips and clammy skin in most cases (4 of 5 cases).

We also reviewed laboratory data in our hospitalized WFS cases (Table 3). In two of our cases blood cultures were performed (case 2 and case 5) and only in one case blood culture was positive for Neisseria meningitidis; in other two cases cultures have not been performed due to the rapid evolution to death. According to the literature blood tests in the peripheral blood

Table 2. Clinical data

Case nr.		*Case 1*	*Case 2*	*Case 3*	*Case 4*	*Case 5*
REASONS FOR HOSPITALIZATION		cyanosis fever dyspnoea moan vomiting green chairs malaise	cyanosis fever cough vomiting malaise		cyanosis fever cough dyspnoea vomiting rapid alteration of the general condition	cyanosis cough , runny nose consuls crisis apnea attacks vomiting chairs greenish diarrhea
PARAMETERS	RF	65-70 resp/min	65 resp/min		-	-
	AV	200-240 b/min	195 b/min		-	187 b/min
	SaO_2 %	76 %	-		-	50%
	TRC	5-6 sec	6 sec		6-7 sec	>5 sec
	t˚C	39.0 ˚C	38.1 ˚C		35.6 ˚C	39.1 ˚C
EVOLUTION	Skin	pale, wet, cold skin petechiae	pale, wet , cold skin petechiae		pale, wet, cold skin petechiae	pale, wet, cold skin petechiae
	Muscle	generalized hypotonia	generalized hypotonia			legs hypotonia
	Lung	bronchial murmurs				bronchial murmurs
	heart	tachycardia impalpable peripheral pulse	low noise			low noise
	Brain	neck stiffness tonic-clonic seizures	generalized hypotonia			hyperactivity opistotonus

Table 3. Laboratory data

LABORATORY		CASE 1	CASE 2	CASE 3	CASE 4	CASE 5
Biochemistry	Urea (mg/dL)		57.79 ↑			9.97 ↓
	Creatinine (g/dL)		1.17			0.60 ↓
	Glucose (mg/dL)	17.0 ↓	44.0 ↓			61.0 ↓
	AST (U/L)		36 ↑			37.0 ↑
	PCR (mg/L)		88.0 ↑			80.6 ↑
	Sodium (mmol/L)	129.0 ↓	128.0 ↓			138.0
	Potassium (mmol/L)	4.80 ↑	4.90 ↑			8.20 ↑
	Blood culture		POSITIVE (N. Meningitis)			NEGATIVE
Coagulation time	Prothtombin time (sec)		56.0 ↑	*SUDDEN DEATH*	*RAPID EVOLUTION*	>180
	Prothtombin time (%)		15.30 ↓			28.0
	INR		5.21 ↓			0.8
CBC	WBC (per mm^3)		7.30			13.40 ↑
	RBC(per mm^3)		2.57 ↓			2.03 ↓
	Hgb	9.9 ↓	6.40 ↓			5.30 ↓
	Hct %	30.5 ↓	19.50 ↓			17.80 ↓
	NEUT %		20.70 ↓			39.10 ↓
	LYM %		74.90 ↑			35.30 ↑
	PLT (per mm^3)		48.00 ↓			11.10 ↓
Oximetry	ph	7.32	7.0 ↓			6.81 ↓
	pCO2 (mmHg)	20.1	74.7			174.7
	pO2 (mmHg)	21.2	46.3			32.5

Table 4. Histopathological findings

	BRAIN	*PALATINE TONSILS*	*LUNG*	*HEART*	*LIVER*	*KIDNEY*	*ADRENAL GLAND*
1.	Anemia cerebral edema leptomeningitis		hyperemia emphysema area interstitial pneumonia			the usual structure	massive haemorrhage
2.	cerebral edema Capillary leucostasis		interstitial pneumonitis capillary leucostasis			stasis	massive haemorrhage
3.	cerebral edema capillary leucostasis		Interstitial pneumonia bronchopneumonia		minimum lymphoplasmacytic inflammatory infiltrate the portal space	pyelonephritis	massive haemorrhage extensive necrosis
4.	*cerebral congestion*	hyperplasia of follicles with germinal centers	emphysema	No pathological changes	lymphoplasmacytic inflammatory infiltrate the portal space	stasis	massive haemorrhage
5.	perineuronal and perivascular cerebral edema Capillary leucostasis	inflammatory infiltrate	interstitial pneumonia capillary leucostasis		lymphoplasmacytic inflammatory infiltrate the portal space		massive haemorrhage extensive necrosis

Table 5. Histopathological findings

Cerebral edema	Temperature	Case Nr.	Time	Adrenal necrosis
+	39.0℃	1	1 h 40 min	
+	38.1℃	2	4 h 55 min	
+	Immeasurable	3	?(~ 8 h)	+
-	35.6℃	4	45 min	
+	39.1℃	5	8 h	+

cultures are negative in the first 24 hours and in 50% of cases they become positive later. Further tests described are central blood cultures (CBC), electrolytes dosage, renal function tests and coagulation tests. Causative organism varies by age, immune function, the vaccine status and geographic region. Laboratory tests revealed three phenomena: hemorrhagic syndrome (decreased coagulation factors, decreased platelets)anemic syndrome and post-thrombotic syndrome leading to acute adrenal insufficiency with elements of hyponatremia, hyperkalemia, hypoglycemia and acidosis due to decreased cortisol and increase of the andrenocorticotrop hormone (ACTH) [14]. Leukocytosis with white blood cell counts deflection to the left side is common in all the cases, especially leukocytosis with eosinophilia. Another important criterion for the pathogenesis of this syndrome is the increased metabolic anion gap due to acidosis hyperkalemia by loss of cortisol, which affects the ability to remove free water from the organism resulting in fatigue and tachycardia. Hyperkalemia is commonly associated with disseminated coagulopathy [19, 20].

Another change is the diminution of blood platelets, prothrombin time and INR which explains the disruption of coagulation factors and occurrence of disseminated coagulopathy. Increased C-reactive protein (CRP) occurred in 4 of 5 cases is an important indicator of inflammation, but does not give any information about the location of the inflammatory process. This increased CRP, associated with slightly decreased red blood cells, hematocrit and hemoglobin renders intra-infectious anemia,process observed in 4 of 5 cases. Loss of cortisol also decreases gastrointestinal motility and secretion, as well as the absorption of iron and vitamin B12, which could explain anemia. We observed increase in red blood cells in urine in one of our cases, similar to a case from the literature [19].

Macroscopic changes at autopsy. On external examination we did not found injuries in any of our cases; instead, characteristic petechiae were noted, which ranged in size from petechiae sized a few millimetres in diameter to large petechiae which during a few hours become confluent, resulting in purpuric areas (“flowers of death”) that do not disappear to digital pressure and in some cases become necrotic.

Purpura fulminans is rare and occurs frequently in infants and young children, but can also be a rare manifestation in adults when associated with severe infections. For example meningococcal meningitis is complicated by purpura fulminans in 10-20% of cases among children. Purpura is associated with acquired congenital deficiency of protein C / S which occurs in 1: 500000-1000000 live births. This deficiency can be

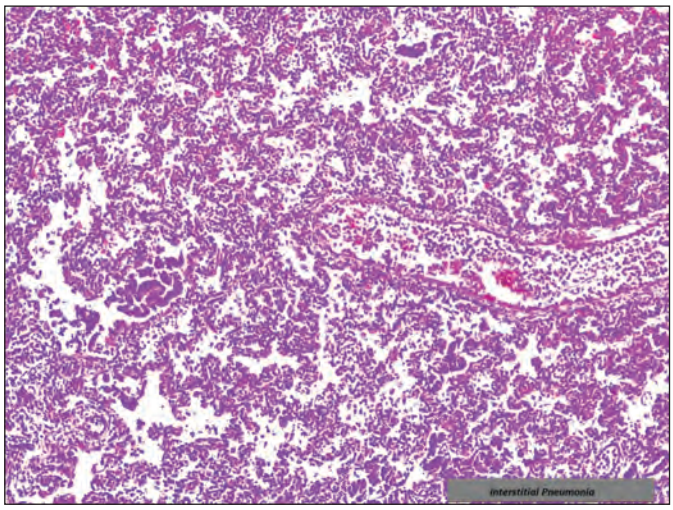

Figure 1. Interstitial pneumonia (HE stain, ob. 10x).

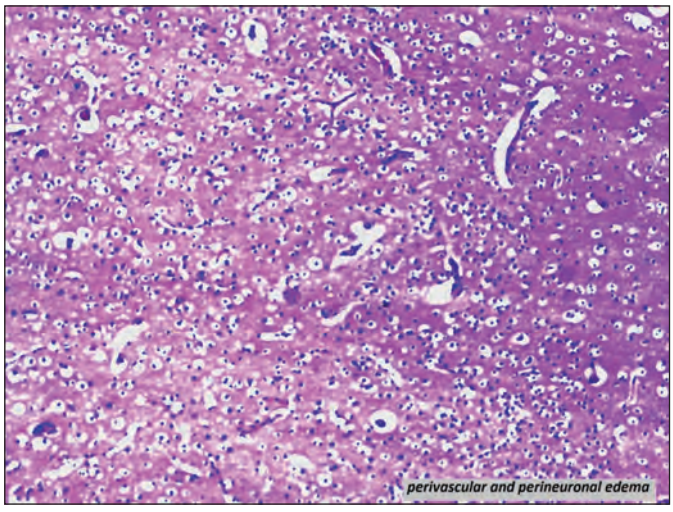

Figure 2. Cerebral edema (HE stain, ob. 10x).

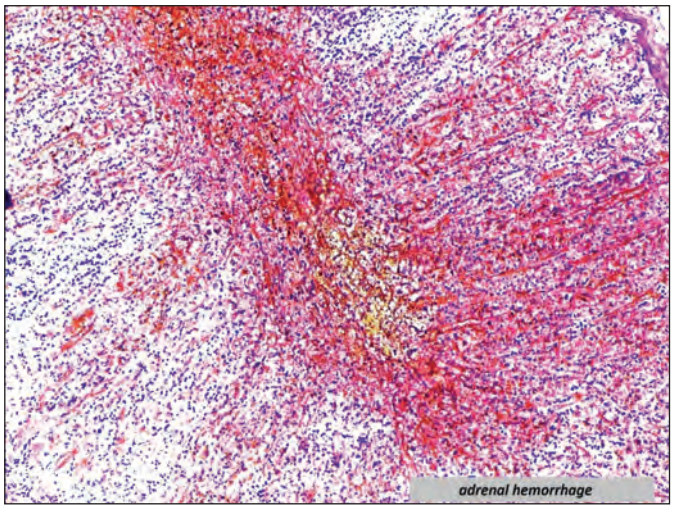

Figure 3. Adrenal hemorrhage (HE stain, ob. 10x).

caused by any depletion of plasma protein C or protein C synthesis decrease (caused by the administration of antagonists vit.K, liver failure complications of prematurity) [21]. Adrenal gland has a rich arterial vascularization, as opposed to the venous one which is limited to a single vein. In stressful situations the secretion of ACTH increases, which stimulates arterial blood flow, overcoming the venous drainage capacity with the occurrence of bleeding. Moreover, the adrenal vein spasm triggered by catecholamines in circulation in stressful situations and tromobosis triggered by coagulopathies leads to venous stasis and haemorrhage.

External examination did not reveal any traumatic injuries, but this does not exclude the traumatic nature of adrenal hemorrhage in cases when a child abuse is suspected. In such cases bleeding are more common at unilateral level than bilateral level [8, 22], especially at the right adrenal gland due to its position and shape they occupy of small space between the spine, liver and inferior vena cava.

At autopsy the pathognomonic change was seen in all 5 cases, namely the adrenal bilateral hemorrhage. Adrenal hemorrhage may be caused by microorganisms other than N. meningitidis and is indicative of sepsis, which can be potentially caused by Gram positive or negativepathogens.In addition to the brain it was not foundepidural infiltrated blood, subdural, but leptomeninges presented in 3 cases a vivid hyperemia[14]. Cerebral edema was present in all cases examined, together with multiorgan congestion. Tonsils in all cases showed marked redness and increased size. We observed left tonsillar necrosis in case 1 and hyperplasia with germinal centers in case 4. The thymus showed an increase in size, spleen and heart and did not present changes neither macroscopically nor microscopically.

Microscopic examination (hematoxylin-eosin stain) revealed heavy adrenal bleeding, in two cases also associating necrosis. In 3 out of 5 cases leucostasis in brain capillary was described. A feature of our cases is the presence of cerebral edema (perineuronal and perivascular) and interstitial pneumonia in 4 out of 5 cases (Table 4, Figs 1 and 2). Compared to the literature data, none of our cases showed signs of macroscopic or microscopic lesions of myocarditis or endocarditis [17] and only one case presented serous leptomeningitis [19]. In the liver we have observed moderate lympho - plasma cell inflammatory infiltrate in the porte spaces in 3 out of 5 cases and also present at tonsillar level in case no. 5.

In our case series we observed a possible correlation between the presence of cerebral edema and febrile cases; on the other hand, emergence of adrenal necrosis seems to be related to a prolonged evolution (with possible prolongation of fibrin deposition in the microcirculation thrombosis and fibrinolysis).

CONCLUSIONS

Waterhouse – Friederichsen syndrome in infants and small children occurred predominantly in male gender, rural areas and seems to be linked to a poor socioeconomically situation. WFS average annual incidence was about 6:100.000 population aged 0-2 years. Time from onset of symptoms to death ranged from 45

min to 8 hours, all children previously having a form of infectious respiratory pathology. Clinical aspect was similar to a respiratory virus infection or enteritis. Rashes, brain edema and interstitial pneumonia were most frequently encountered changes.

Adrenal necrosis correlated with prolonged evolution of symptoms, while cerebral edema appeared in febrile cases evolving in a few hours.

Unlike other reports in the literature, we found no myocardial inflammatory changes in any of our cases. Positive microbiological examination was present in one case (*Neisseria meningitidis*).

Conflict of interest. The authors declare that there is no conflict of interest arising out of this manuscript.

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