Pulmonary thromboembolism in infant: postmortem diagnosis

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Abstract: We present an unusual case of pulmonary thromboembolism diagnosed microscopically in an 8-month-old infant that was victim of an accident and suffered a cranio-cerebral trauma for which he was transported to the emergency department where death was declared shortly. We believe the pulmonary modification was not related to trauma and did not intervene in thanatogenesis. A review of the literature revealed that idiopathic thromboembolism in the pediatric population is relatively infrequent and is almost always associated with an underlying disease or risk factor. Both congenital and acquired conditions contribute to the development of thrombosis. The highest incidence is during the neonatal period, followed by another peak in adolescence. The annual incidence of thromboembolism is 0.007 to 0.14 per 10000 children or 5.3 per 10000 to hospital admissions of children and 24.0 per 10000 admissions to neonatal intensive care units.

Key words: infant, posttraumatic state, pulmonary thromboembolism

The reduced capacity of generating thrombin, the increased capacity of α2-macroglobulina to inhibit thrombin, the increased anti-thrombotic potential of the vessels wall, seem to contribute to the reduced incidence of venous thromboembolism (VTE) in childhood. Still, VTE is more frequently diagnosed in children. The yearly incidence is of 0.07 up to 0.14 in 10 000 children, or of 5.3 in 10 000 hospitalized children, and of 24 to 10 000 newborn babies hospitalizations in the intensive care units [1, 2]. The highest incidence is during the neonatal period, followed by another climax during the teenage period. The patients in the paediatric units of intensive care or those in oncology are very much exposed to the risk. The female teenagers present a rate of VTE twice as higher than in the boys’ case. This thing seems to be caused by the usage of orally administrated birth-control pills and to the pregnancy [3].

Risk factors. Idiopathic VTE in the paediatric population is of a relatively low frequency and is, most of the times, associated with a risk factor or a basic disease. Both congenital states and the acquired ones contribute to the incidence of thrombosis. More than 90% of children with VTE will have ≥2 predisposal factors [4].

Congenital states. The congenital post-thrombotic states in paediatric patients include the mutation of the V Leiden factor, the mutation of the prothrombin gene and disorders of the antithrombin III, of the C protein and of the S protein, with the more prothrombotic homozygote variants. The incidence of the V Leiden factor is between 0% and 5% in the general population, with higher prevalence among the Caucasians. Both the homozygote form and the heterozygote

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one of the V Leiden factor may cause VTE in children, usually in the presence of an acquired risk factor [5]. The mutation of the prothrombin gene is a second mostly met inherited default, in relation to VTE. Its incidence is of ≈2% in the Caucasian population and of 4% till 5% in the Mediterranean population [6]. Two small studies describe the incidence of antithrombin III disorder of 1-3% [7]. The role of other potentially thrombophilic states, among which, hyperhomocysteinemia an the high levels of VII,VIII,IX,XI factors and the lipoprotein have not been established in the paediatric population.

**Acquired states.**

The presence of the central venous catheter (CVC) is the mostly spread acquired releaser for VTE incidence in children, contributing to >90% of all venous thrombosis cases in new-born babies and to >50% of all cases in other age groups [3]. Other acquired states associated with thrombosis in new-born babies include perinatal asphyxia and hypovolemia. In paediatric population, other risk factors include malignity, trauma, surgical operation, the hormone therapy and lupus. The risk for VTE is significantly increased with a CVC in the femoral veins or under the clavicle, suggesting that it would be better to place catheters in the brachial and jugular veins [8]. The external tubes and the large diameter seem to be associated with higher risk for VTE, especially in patients under oncology situations [9].

The Acute lymphoblastic leukaemia (ALL) represents the most common neoplastic process associated to thrombosis, in children.

The VTE percentage in childhood varies from 1.1% and 36.7% with a total average of 3.2% [10]. VTE seems to be an unusual event in children with brain tumours (reported percentage of 0.64% and 2.8%), although it is the second malignity condition as frequency in this age group [11]. The CVC disturbance contributes to the thrombosis incidence in children with brain tumours and seems to reduce the total surviving [11].

Children with various types of malignity, with no ALL and VTE end to be elder (>9 years), are more likely to have VTE at far places from CVC, and are less likely to have inherited prothrombotic mutations [12].

The acquired clinical states may be momentary or may last in time. The momentary clinical states include use of oestrogen in high doses, chicken pox and the neurotic system [13].

**Cases study**

On the 16th of June 2008, a 8 months old girl was admitted in UPU1-SMURD Tg. Mureş (o.c.215519/2008) in non-resuscitable cardiac arrest (asystolia). A post-nutritive aspiration syndrome was the initial assumption. The preliminary official inquiry (The Police of Tg. Mureş Municipality, The Criminal Investigations Office file no 1123/b/2008) suggested that the infant fell from the pram. The mother stated that while the child was held in her arms a cradle bounced by another little girl hit the baby in the head. The family and personal medical history provided no significant elements.

The medico-legal examination of the body highlighted the presence of several traumatic lesions: ‘V’ shape bruising in the right temporal-parietal region, with the tip temporally placed, the lower arm of the lesion being of 4.5 x 0.5 cm, and the hindmost one of 3.5 x 0.5 cm. In the frontal region on the median line there is a bruise of 0.6 cm diameter. The nasal pyramid in the median line presents a purplish bruise of 3 x 2.5 cm. On the level of the right knee there is a semi-circular bruise of 5 x 0.5 cm.
The internal examination revealed an extensive temporo-occipital epicranial haemorrhage; at median occipital level there is a comminuted fracture of the occipital bone (medial location), with multiple irradiated fracture lines (to the right temporal, to left temporal, to the skull base). Shiny, ivory white dura mater, smooth internal surface. Free extra and sub-dural spaces.

The leptomeninges with multiple focal haemorrhages covering the convexity of both cerebral hemispheres. The vessels on the basis of the brain with normal course, no morphologic modifications. Apart from a significant diffuse oedema no significant morphologic modifications were observed in the brain. The cerebellum, the brainstem with no macroscopic modifications. The cerebral ventricles were symmetric, of normal volume and containing clear CSF. Tracheo-bronchial aspiration of gastric content in reduced quantity.

The histopathology examination revealed massive brain oedema (fig.1), moderate leptomeningal haemorrhage (fig.2), brain anaemia.

In the heart, subendocardial haemorrhages (fig.3), some myocytes with vacuolar dystrophy, scattered foci of myocardial lymphocytic infiltration (fig.4). Pulmonary distelectasia and thromboembolism (fig.5).

The macroscopic and microscopic data, led to the conclusion that death was determined by a cranial trauma with comminuted skull fracture, leptomeningeal haemorrhage, brain oedema and pulmonary thromboembolism.

The traumatic lesions could be produced by a direct hit by a tough body of big mass and weight, most likely a cradle in motion and compression between two hard surfaces.
Discussions

The mortality percentage for all causes in paediatric patients vary between 14% and 23%, with mortality because of VTE of 1% up to 2% [1,14], reflecting the seriousness of the clinical states that stand on the basis of this type of population. After 3 years of pursuit the cumulative emergence of a VTE recurrence is of ≈9% with a study reporting a percentage of 21% [15].

The VTE recurrence risk after a special spontaneous thrombotic event seems to be more significant in patients with anticoagulant lupus or in those who carry a congenital pro-thrombotic risk factor or a mixture [15]. The high levels of VIII plasmatic factor, D-dimer, or both, to the diagnosis, and a persistent increase of at least one of these factors after the anticoagulant therapy for a standard period of time, have in view a weak result in

Fig. 3 Myocardial hemorrhage, vacuolar dystrophy. (Hpt.nr. 19591/2008, col. HE x100)

Fig. 4 Lymphocytic myocarditis (Hpt.nr. 19591/2008, col. HE x100)

Fig. 5 Pulmonary thromboembolia (Hpt.nr. 19590/2008, col. HE x100)
children with thrombosis [16].

The post-thrombotic syndrome (PTS), which stands in pain, inflammation, skin pigmentation and, sometimes, the leg ulceration is an important complication of VTE paediatrics. At least one third of the patients have PTS incidence, which can go up to 60% [17]. Yet, PTS in paediatric patients is usually light with increased circumferences of the members, inflammation, varicosity, pain and pigmentation. Few patients develop venous ulceration. The risk factors for PTS incidence are fuzzy. The combined fibrinolytic and anticoagulant treatment may reduce PTS [18].

**Diagnosis.** The clinical presentation of VTE depends on the location of thrombi. Most of the paediatric venous thromboses are linked to catheters and thus they are located in the upper venous system. Many of them are asymptomatic. When the symptoms occur they might include inflammation, pain and the discolouring of the upper extremity, the syndrome of upper vena cava, chylothorax and chylopericardium. Usually, VTE in the lower extremity causes abdominal, inguinal pain or pain in the leg, abdomen or leg inflammation and a red or purple-blue colouring of the lower extremity. The sepsis and the repeated loss of the tube opening raises suspicion on the catheter related thrombosis [4]. The chronic catheter related thrombosis appears, sometimes, with collateral circulation. At some new-born babies, thrombocytopenia seems to be the only sign of VTE because of thrombocyte consumption. The deficiency in homozygote C and S proteins may appear as neonatal fulminate purple, characterized by fast-evolution purple and bruise, the incidence might be, sometimes, as huge skin necroses with pustules.

The compression, together with Doppler venous ultrasonography is the most often used way for the diagnosis of proximal vein thrombosis in the lower extremity and the extra-thorax area, the upper extremity in children. CT with intravenous contrast is used to assess the superficial venous system and the abdominal and pelvic system.

The ventilation perfusion, lung scanning and CT with contrast [19] are used for the diagnosis of pulmonary embolism, while MRI and angiography are used to assess the intracranium venous system, the superior vena cava and the neighbouring sub-clavicle veins. The echocardiograph might detect cardiac thrombi or thrombi in the proximal upper vena cava and might assess the right ventricular function. The venography based on draining tube is rarely used because of technical difficulties which are a real challenge [20]. The levels of VIII factor and D-dimer may be useful in the monitoring therapy and in establishing the duration of the treatment.

**Prophylaxis.** It is not yet recommended the routine prophylactic anticoagulation for VTE in children with central venous catheter (CVC), since the clinical relevance of these primary asymptomatic thrombi is not known and does not need yet to be assessed [4]. The prophylactic anticoagulation is useful in children with congenital thrombophilia, who are in very risky situations, as might be, after trauma or surgical operation or during limited period of times when they are exposed to a risk, such as severe infection or the CVC presence. The usage of adequate compressor stockings and fighting against co-morbid causes such as obesity will prevent from appearing sequelae, such as PTS [4].

**References**