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Original Article

VASCULAR THROMBOSIS IN CHILD CARE PRACTICE

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Abstract

Although relatively frequent in adult care practice, thrombotic stroke is quite rare in child care practice. The authors analyze the diagnosis and treatment difficulties of vascular thrombosis in children, in terms of their own clinical practice.

Keywords: *Pediatric venous Thrombosis, Nephrotic syndrome, Lupus, Treatment*

Rezumat

Accidentul vascular trombotic, relativ frecvent în patologia adultului, este relativ rar în practica pediatrică. Autorii analizează prin prisma cazuisticii proprii problemele de diagnostic şi tratament în trombozele vasculare la copil.

Cuvinte-cheie: *Tromboza venoasă la copil, Sindrom Nefrotic, Lupus, Tratament*

General considerations

Vascular thrombosis represent a rare failures in medical practice of the child.

The polymorphism in the etiology, the relative rarity and semiologic complexity make the performance of homogeneous trials difficult, so that the discussion and diagnosis and therapeutic standardization are still in the phase of desideratum. Its high severity, "life threatening", determines the agglomeration of these cases in special intensive care units, so that the approach becomes particular to them.

A point of view from the patient's age, vascular thromboses of the child are divided in two groups:

A. Neonatal vascular thromboses

B. Infant and child vascular thromboses

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We consider that the etiology approach is the main advantage of this classification. Therefore the neonatal vascular thromboses are favoured and precipitated by the age particularities (in the "classical" textbooks, the newborn is characterized as suffering from hypothermia, and being at risk for bleeding and hyporeactivity). Circulatory system changes at birth, neonatal infections, venous catheterization (especially the umbilical one) required during reanimation and therapy of severe conditions (septicemia, respiratory distress syndrome), as well as the hypercoagulability caused by polyglobulia and fibrinolysis reduction are determinant factors of vascular thromboses. Vascular thromboses are most frequent in neonatology and have various etiology factors; there are two main causes: sepsis and venous catheterization - umbilical ones especially. Renal vein thrombosis, which occurs quite frequent, is generally masked by the main disease, so that the diagnosis is late, after remission, if it was unilateral or with acute renal failure, and the diagnosis is made at ultrasound (enlarged kidneys, with loss of corticomedular differentiation and absence of Doppler signal). Thrombosis of the trunk of inferior vena cava, an extremely severe complication, usually has a poor prognosis, being incompatible with survival. Portal vein thrombosis – an "extension" of umbilical vein thrombosis, secondary to catheterization and/or administration of hypertonic solutions at this level – is discovered later during history taking when the etiology of prehepatic portal hypertension (Banti syndrome) is investigated.

The arterial thromboses severity index is highest per se and also because of its trigger. The newborn is in severe shock, with extreme palor and visible "gangrene" type thromboses of the extremities (fingers, nose, ear) and echo-Doppler examination reveals the unilateral or bilateral renal artery thrombosis as part of aortic thrombosis (a complication usually incompatible with life). Other localizations are the mesenteric ones, with intestinal necrosis and/or iliac or brachial arterial axes.

The infant vascular thromboses are complications of hypovolemia from dehydration and/or septicemia, the prerenal acute renal failure being the one that provides the clinical spectrum of the case. The hemolytic uremic syndrome is the other etiology that generates vascular thromboses in infant-child age group, with different locations, from the mesenteric and cerebral ones to the coronary location, responsible for the sudden death; other cause of coronary death in children is Kawasaki syndrome.

Vascular thromboses may occur in child during the following illnesses:

- nephrotic syndrome
- disorders of hemostasis
- collagen diseases with positive LA
- primary antiphospholipid syndrome
- factor V Leiden syndrome
- paraneoplastic syndrome
- septicemia
- multiple trauma
- surgery
- central and/or peripheral venous catheters with therapeutic role (thrombosis is secondary to their thrombozation and/or incorrect use).

The main causes of venous thrombosis in children, by M. Robin, C. Bayer 1987, cited by Ellis D. Avner, William E. Harmon, Patrick Niaudet (1)

Local factors	**General pathology**	**Constitutional diseases of hemostasis**
Direct venous agression *- venous puncture* *- central catheters* *- ventricular derivation catheters*	Drugs that modify the hemostasis *- oral contraceptives* *- asparaginase*	Constitutional deficit *- ATIII* *- Protein C* *- Protein S*
Venous compression *- plaster* *- fractures*	Nephrotic syndrome Inflamatory diseases *- SLE* *- Ulcerative colitis* *- Crohn disease*	Plasminogen anomalies *- hipoplasminogenemia* *- displasminogenemia,* *- defect of tissue plasminogen activator release*
Perivenous inflamation secondary to infection *- osteomyelitis* *- ENS infection* *- brain venous thrombosis*	Metabolic Diseases *- Homocisteinemia* *- Hyperlipemia* Septicemia *- Staphylococus* *- Candida* *- Streptococus*	
Venous malformations *- agenesia, hipoplasia or ectasia of the profund truncks* *- Membranous obstructionof vena cava*	Other general factors: *- surgery* *- malignant diseases* *- cardiac failure* *- obesity* *- bone marrow involvement* *- physical effort, trauma*	

The diagnosis of vascular thrombosis essentially assumes the recognition of their possible existence and their search; the diagnosis implies the whole medical team involved but also adequate access to medical technology, diagnostic screening.

Diagnosis

Anamnesis should follow two directions: the family history (most hereditary thrombotic diseases have an autosomal dominant transmission with exception: homocisteinemie, plasminogen activator deficiency) and the significant pathology (acquired etiology of thrombosis): antiphospholipid syndrome, nephrotic syndrome, primary autoimmune disease, SLE, Malignancies, Liver Diseases, Renal failure, Sickle cell anemia, DIC, PTT, inflammatory bowel disease. (2)

Establishment of the site and extension of the thrombosis:

- Non-invasive: Eco Doppler, CT scan, MRI

Laboratory diagnosis of coagulation: positive inflammatory tests, Functional tests for identification of various anticoagulants factors deficiency (AT III, protein S, protein C), raised PDF, raised D dimers

Protein C Deficiency

- Protein C = vitamin K dependent plasma glycoprotein, (synthesis encoded by a gene located on chromosome 2) which was activated functions as an anticoagulant by inactivating FVa and FVIIa (anticoagulant effect)
- It neutralizes the inhibitor 3 of the plasminogen activator
- Plasma levels below 50% (normal range 70-100%) = Thrombosis
- Inherited - autosomal dominant
- The prevalence in the general population: 1:500
- Subdivided into 2 types: Type I Deficiency (low activity and low antigen level) - quantitative, and Type II Deficiency (low activity and normal antigen level) – qualitative
- Patients: homozygous and heterozygous – they have prot C serum levels ~ 50% (they can be asymptomatic or require additional risk factors - pregnancy, estrogen)
- In homozygous newborns may cause a fatal thrombotic disorder, which may present with neonatal purpura fulminans or CID
- Diagnosis is made on functional tests (for both types) and immunological tests for type I

(3)

Activated protein C resistance (Factor V Leiden) - identified in 1993

- The most common hereditary predisposition to thrombotic disease
- 20-60% of all patients with recurrent thrombotic complications
- Transmission autosomal dominant
- Breakpoint mutation in the position 1691 of the nucleotide chain that is coding the synthesis of factor V gene (identified in 1994)
- FV Leiden can’t be degraded by activated protein C
- Homozygous – by 80 times the risk of thrombosis is higher than the general population
- Heterozygous – by 7-8 times higher risk of thrombosis compared to the population. The risk increases if there are complementary risk factors, genetic or acquired ones: Pregnancy, Contraceptives, Surgery, Trauma
- Clinic - venous thrombosis with different locations

AT III deficiency:

- Transmission: autosomal dominant
- Prevalence in general population: 1:600
- Type I (quantitative deficiency, only heterozygous) - parallel decrease in AT III levels, measured both by functional and immunological tests. It is a gene mutation / deletion, leading to the decreased protein synthesis
- Type II (qualitative deficiency, hetero / homozygous) - breakpoint mutations leading to synthesis of abnormal proteins. Decreasing of AT III activity in functional tests (normal immunological tests) associated with normal amounts of protein
- acquired AT III deficiency: Liver diseases, Nephrotic syndrome, CID, Treatment with oral contraceptives

(4)

Protein S Deficiency - described in 1984

- Protein S - vitamin K dependent plasma protein that mediates the activity of activated protein C, acting as a cofactor in the inactivation reaction of the FVa, FVIIIa and has an inhibitory action on FXA.
- Inherited - autosomal dominant
- Subdived into 2 types:
  - Type I Deficiency (low activity and low antigen level) – quantitative
  - Type II Deficiency (low activity and normal antigen level) – qualitative
- Patients: homozygous (rare) and heterozygous (majority), ~ 50% level

(5)

- In the severe forms - purpura fulminans
- Diagnosis:
  - Screening tests for coagulation are normal
  - The measure is indicated only after exclusion of activated protein C resistance
  - Immunological tests - for quantitative levels of total protein and free fractions

As long as the diagnosis of vascular thrombosis is established, the next step is to determine the location, extension and type of affected vessels: artery (main trunk, side branch), vein (main trunk, side branch), capillary territory, Lymphatic Drainage System.

The level of damage related to the affected organs organ / organs and, consequently, the functional prognosis and / or life depends fundamentally on these data.

(6, 7)

Treatment

The treatment of vascular thrombosis represents a major emergency, the most important factor that influence the early and late prognosis is the period of timebetween the onset and the diagnosis (ischemia, irrigation disturbances). The prevention implies the recognition and the evaluation of the favourable conditions and the establish of the therapeutic measures. Considering all these points we may conclude that it is necessary to treat both the underlying disease and the proper thrombosis.

Thrombectomy – thrombolisis is the mainstain of the therapy. Unfortunately, the late diagnosis or the unfavourable factors like the site and the extension of the thrombosis are the causes of the illusory radical solution.

From a synthetically point of view, the treatment strategy consists of:

- Heparinotherapy
- Oral anticoagulants
- Thrombolitic treatment (fibrinolitic)
- Surgical treatment
- The vena cava filter

Thrombolytic agents are difficult to handle, there is no standardization of doses and ways of administration (doses, duration) and, last but not least, they are not always available at the right time. Their strategy and their unique properties related to their use are set as follows:

Throbolithic agents

- **Streptokinase.** Dose: 4000-6000 UI/BW iv push in 30 minutes, followed by iv infusion 1400-2000 UI/BW/hour for 24 – max 72 hours. It could determine hypersensitivity. It is metabolised by antibodies (patients with a history of streptococal infections or the newborn with maternal antibodies)
- **Urokinase Dose:** 4400 UI/BW iv push in 20 min, followe by iv infusion 4400 UI/BW/hour – 12 hours. It doesn't cause hypersensitivity. It is not metabolized by antibodies.

Monitoring the Streptokinase and Urokinaze treatment: Thrombin Time (8, 9). Effectiveness – increases aPTT 2-5 times

- **Tisular activator of fibrinogen.** It is produced in the human body by the vascular endothelium and industrial produced using recombinant technology. Dose – 0,1-0,5 mg/bw/hour

(10)

New thrombolythic agents

- APSAC – unisolated plasminogen SK activator complex
- Pro-urokinaze
- Therapeutical indications in thrombosis: Effective just in case of early administration (first 24-48 hours). Greater risc of hemmorhage than heparine

Under these conditions, anticoagulant therapy is usually a heparin one (intravenous or oral), the main features being the following:

Heparinotherapy: The anticoagulant effect of heparine is not a direct one, but it is done through AT III.

Types of heparin: *Unfractionated* (standard) heparin, *Low molecular wight heparin* (enoxaparine, deltaparine, nordraparine) (LMWH)

- *Unfractionated (standard) heparin:*
  - endovenous
  - Half-time = 1-2 hours
  - Inactivated in the liver
  - Renal excretion
  - The action is related to the endothelial cells and plasma proteins binding
  - Facility of using
- *LMWH*
  - Half-time: 2 times longer
  - More reduced endothelial and plasma protein binding
  - Subcutaneous byodisponibility is 3-5 times higher
  - Administration does not need laboratory monitoring

Dosing of heparin: Adolescents /elder children – 5000 UI iv push afollowed by 30.000 UI/24h, during the first 24h, then 10.000-20.000 UI every 12 hours, for 5-10 days. Young children – 50 U/Kg iv push, followed by 10-15 UI/bwh/hour infusion, or 75-100 UI/bwh every 4 hours. Enoxparine dosing – 2,5 mg/Kg/day, sc, or 1 mg/kgc x 2/ day, sc

Monitoring TPT at every 6 hours, then daily from initiation. TPTa - 1.5 to 2.5 x N

Complications:

- Major bleeding (5-7%)
- Decreased ATIII
- Thrombocytopenia (6%)
- Thrombocytosis (0.2%)

Overdose heparin - protamine sulphate (PS): 1 mg PS - 1000 IU heparin
(11, 12)

Oral anticoagulants are drugs that inhibit hepatic biosynthesis of Vitamin K - dependent coagulation protein (II, VII, IX, X, C, S)

Features: binds to albumin, metabolizes in the liver, has a half time ~ 36 hours, reach effective serum level after 4-5 days of treatment initiation (13)

Monitoring of prothrombin time / INR, with a goal of INR = 2-3

Dosing of warfarin - 0.1 to 0.15 mg / *Kg* / day (max 10-15 mg / day) - loading dose, then maintenance 2-10 mg / day, depending on INR

Adverse effects: Hemorrhage, Skin necrosis

In case of overdose - Vitamin K, PPC
(14, 15)

Surgery remains elusive in the vast majority of cases because of the exceeding of the optimum duration, but also due to the location and the extent of thrombosis and / or the access to appropriate filter.

Material and method

The Department of Nephrology and Pediatric Dialysis of Fundeni Clinical Institute was established within the Pediatric Clinic Fundeni in December 1992 when the first hemodialysis was performed in a 4 years 10 months old child suffering of hemolytic-uremic syndrome. Today this department is integrated part of Uronephrology and Renal Transplantation Fundeni.

Between 1992-2000 we diagnosed and treated in our Department more than 1800 pediatric patients suffering of renal pathology (in 24 beds, 5 posts of hemodialysis and 2 posts of peritoneal dialysis). Out of these 28 children or 1.55% presented various vascular thrombosis. From an ethiologic point of view the statistics are as follows:

1. Systemic lupus erythematosus (S:LE): 7 out of 110 patients (6.36% of the patients with SLE or 0.38% of the total patients in the study)
2. Sepsis: 5 out of 28 patients (17.85 of the patients with sepsis or 0.27% of the total patients in the study)
3. Paradoxal thrombosis (patients with thrombocytopenia <50.000/mmc with malignant desease, who develop vascular thrombosis as part of the paraneoplastic syndrome): 5 out of 537 patients (0.93% of the mentioned subgroup or 0.27% of total)
4. Nephrotic syndrome with clotting disorder (thrombocytosis, hyperfibrinogenic anemia, LA positive): 4 out of 137 patients (2.91% of the patients with nephrotic syndrome or 0.22% of the total)
5. Hemolythic-uremic syndrome: 3 out of 53 patients (5.66% or 0.16% of total)
6. Primary clotting disorders - anti phospholipidic syndrome: 3 out of 15 patients (20% or 0.16% of the total)
7. Major circulatory disorders: 1 patient with bacterian pericarditis (staphylococcus) with inferior vena cava thrombosis (0.05 % of the total patients in the study)

As it may be noticed, SLE has the highest incidence of vascular thrombosis, also due to the high number of patients. The patients diagnosed with SLE underwent a complex and standardized therapy, consisting of an induction phase and maintenance phase, using multidrug therapies: puls-therapy with Cyclophosphamide, cortisone puls-therapy, oral corticotherapy, Azothioprin or Mycophenolate Mofetil, Ciclosporin. 7 patient underwent trough plasmaferesis, 3 of them presenting with severe CNS symtoms (seizures, coma).

Vascular thrombosis in SLE manifested as follows a one patient (R.M., age 16y, female) with capillary thrombosis and secondary necrosis of three phalanxs of the hand and 2 of the legs, also right atrial thrombosis *(figure no.1, 2),* a 3 patients with cerebral microthrombosis, a one patient with popliteal thrombophlebitis, one patient with femoral thrombophlebitis and a one patient with axillar thrombophlebitis.

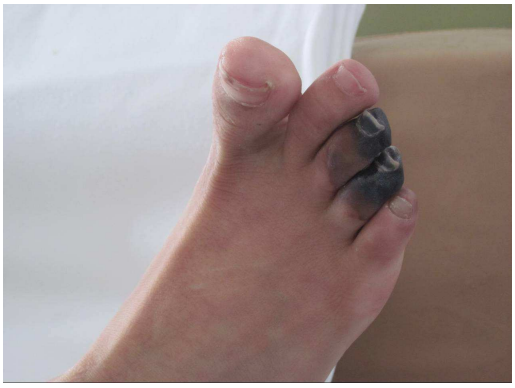

Figure no.1. *Necrosis of two phalangs of the leg due to Vascular thrombosis in Systemic Lupus erythematosus*

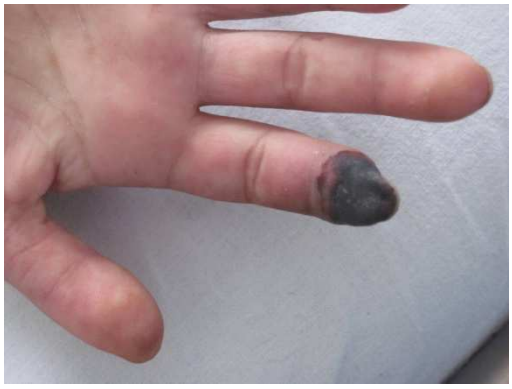

Figure no.2. *Necrosis of right index due to Vascular thrombosis in Systemic Lupus erythematosus*

In all these cases treating vascular thrombosis was a major emergency and consisted of iv Heparin or subcutaneous LMWH followed by oral Warfarin. After stabilization it was followed by maintainance treatment with Warfarin/Aspirin and Vessel Due F. For the first of the pre-mentioned cases surgical toilet was performed due to the severity of the necrosis.

Between 1992-2000 we treated 137 patients presenting primary or secondary nephrotic syndrom (the patients were referred to us), in/with a severe condition due to the lack of response to initial therapy and/or important complications. Four of them presented with main blood vessels thrombosis (inferior cava branch). These cases have been diagnosed at the age of primary school/ pre-pubertal. We will present here a patient from Pediatric Clinic, St. Mary, Iasi, Dr. Mihaela Munteanu - for the quality of the prosector images *(figure no.3, 4)*:

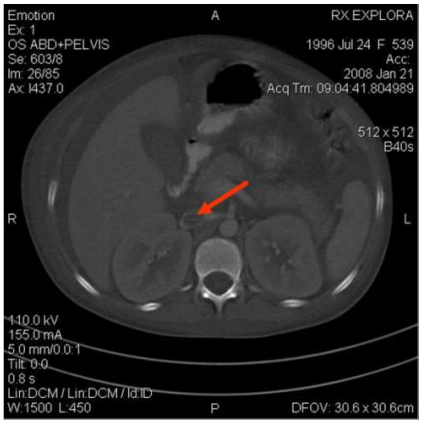

Figure no.3. *Thrombosis of inferior vena cava. Aspect of computer tomography, native examination*

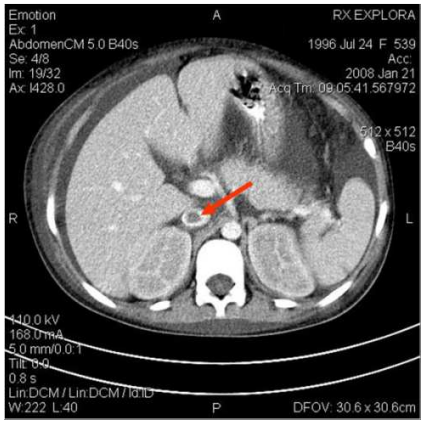

Figure no.4. *Thrombosis of inferior vena cava. Aspect of computer tomography with contrast* Iv *examination.*

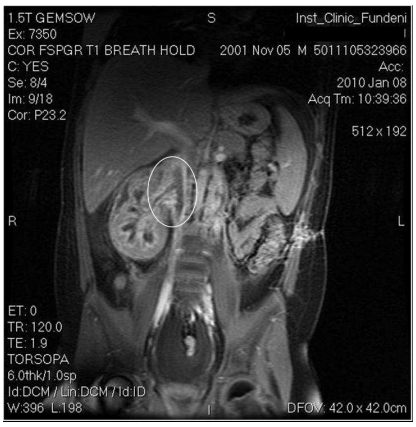

Figure no.5A. *Thrombosis of left renal vein. Aspect of magnetic resonance.*

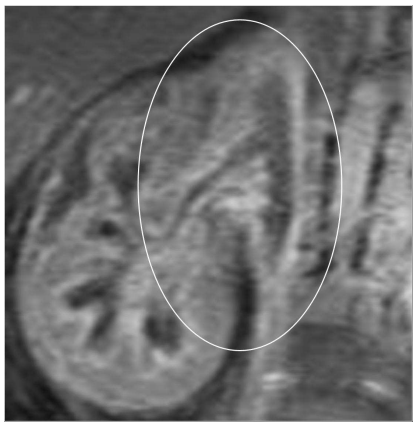

Figure no.5B. *Thrombosis of left renal vein - Aspect of magnetic resonance-detail.*

In another patient a 8 years age, male *(figure no.5A, 5B)*, the nephrotic syndrome had begun atypical with thrombosis of left renal vein (leading to left nephrectomy) followed at 2 weeks by thrombosis of inferior cava branch extended in the right renal vein. Complex tests of the coagulation make the absence of any symtoms until this age and the onset with albuminuria (preceding the thrombosis) lead to labeling as atypical nephrotic syndrom.

In these cases the treatment consisted of:

a) Emergency therapy: iv Heparin, 10 days, followed by LMWH subcutaneous (for 12 days in average) and maintenance therapy with Warfarin and Vessel Due F po.

b) Nephrotic syndrome treatment, emphasizing the hypovolemic therapy - favoring factor of coagulation disorders.

Results and disscutions

The course of the disease for four patients was favourable, achieving vascular re-permeability for all patients (medicative thrombolysis). For the patient with left nephrectomy and thrombosis of inferior cava branch, the evolution to renal impairment imposed the inclusion in the extrarenal filtering program, the chosen method being automatic peritoneal dialysis (vascular aproach with catheter or fistula would have been a risk factor!). This patient for whom was also acquired complete vascular re-permeability, the renal scleroatrophic lesions (highlighted by echography and magnetic resonance) have determined, dialysis dependence' even if a reoccurrence of diuresis was achieved but with reduced urinary concentration.

Hemolytic-uremic syndrom (HUS) represents a heterogenic group of disorders of various etiology but unic pathogeny, which consists of mycroangiophatic hemolytic anemia, thrombocytopenia of consumption and acute renal impairment. Didactic

classification in typical SHU (SHU+diarrhea) and atypical SHU (SHU without diarrhea) permits, besides understanding the pathogenic mechanism with CID involvment in the atypical forms also understanding of the therapeutic strategy.

The use of extrarenal filtering and plasmapheresis together with administrating of PPC, transfusion of red blood cells and hydroelectrolytic and acidobasic rebalance have lead to a significant improvment of prognosis. Practically, nowadays – with few exceptions (where the experience and the equipment are vital) – survival is the norm and the renal function restoration with restitutio ad integrum is expected.

From 1992 until now 53 patients with SHU have been treated in our clinic. For 33 of them (62.26%) extrarenal filtering was used with a mortality rate of 8%; n 5 cases due to the young age less then 9 month, youngest being 1 month old only and the small body size (Weight less then 7 kg) peritoneal dialysis was the the treatment choice. For the other patients we used vascular approach for the speed of the action and possibility to alternate the methods: dialysis/ hemodiafiltering/ hemofiltering.

Plasmapheresis was used as well for 2 patients, unfortunately less successful.

For the patients presenting with SHU, vascular thrombosis manifested as follow an one patient, female, a 5 years, with mesenteric infarction with intestinal loop necrosis, necessitated surgical resection. Acute renal impairment benefited of hemodiafiltering. The course of the desease was unfavourable, turning slowly towards CRI and has been included into hemodialysis program after 10 years from the acute episode. An a two patients had stroke, one died during treatment, the other presents with cerebral atrophy with normal intellect and slightly flaccid legs *(figure no.6, 7).*

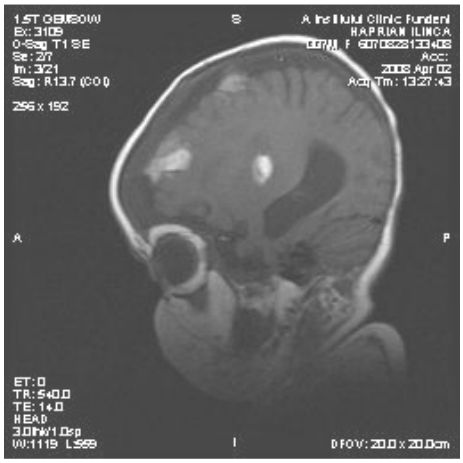

Figure no.6. *Cerebral haemorrhage in the fronto-parietal lobe. Aspect of magnetic resonance*

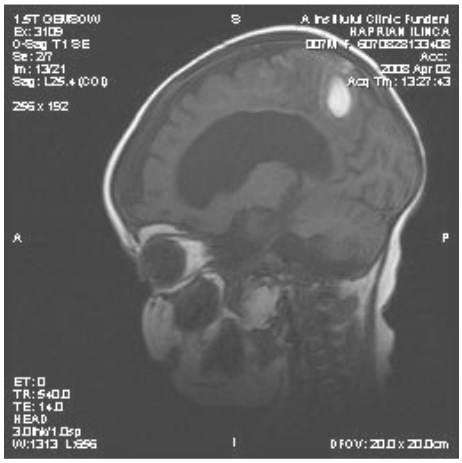

Figure no.7. *Cerebral haemorrhage in the occipital lobe. Aspect of magnetic resonance.*

Another chapter represents vascular thrombosis in the malignant deseases, where thrombocytopenia as manifestation of the medular impairment syndrome is a protective antithrombotic factor, thus the name of this chapter „Paradoxical thrombosis". During 1992-2010, 12 out of 537 oncopediatric patients necessitated extrarenal filtering therapy:

10 due to the tumoral lysis syndrome and 2 for acute renal failure post-renal-abdominal-pelvic tumor. In all this cases the paratumoral syndrome, the tumoral lysis syndrome and the last but not least the chateter for hemodialysis represented the cause of vascular thrombosis. In other 2 cases thrombosis manifested at cerebral level, with unfavourable course of desease. The other 2 patients had ileo-femoral thrombosis, on the catheterizing axis; in these cases iv Heparin therapy led to medicative thrombosis.

Another cause of vascular thrombosis is septicemia with alterations of vascular flow, disseminate intravascular coagulation with/without associated clotting disorders(lack of AT III or Protein S). This was the case for 9 out of 44 children presenting with toxico-septic status. In 3 cases a lack of AT III (2 patients) and Protein S (1 patient) was found. In one of the cases with shortage of S Protein the sepsis caused thrombosis of left axillar vascular axis and right popliteal artery, the thrombolytic therapy with Streptaze (Intensive Care of„C.C.Iliescu" Institute) failing. For another patient the significant disturbance of venous return secondary to a pericarditis has caused the inferior cav branch thrombosis. In the other 7 cases vascular thrombosis manifested as phlebo-thrombosis, being induced by the septic component, being localised at the lower limb level for 5 patients and upper limb for the other 2.

Conclusions

The use of more and more complex technologies in the severe cases, catheterisation maneuvers for diagnostic and/or therapeutical purpose increase the risk of vascular thrombosis-accidental or expected complication but unavoidable in the assisting conditions within intensive care servicies.

Recognition of the thrombogenic conditions and early localisation (Echo Doppler, MRI) is mandatory for an adequate therapy, decisive factor for a favourable outcome.

Due to the relatively rarity of the cases and ethiologic polimorphy it is relatively risky to try a clasification and standardization of the diagnosis and treatment.

After revewing all the available literature it can be stated that vascular thrombosis in children still represents a chapter which is being written from the accumulating clinical experience.

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