SECONDARY THROMBOCYTOSIS IN CHILDREN

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Abstract: *Secondary thrombocytosis is defined as a growth of platelet number over 440.000/mm3 or more than 2 standard deviations, secondary to a primary disease like iron deficiency anemia or an infection. It is frequently observed in children, especially in infants and young children, often randomly discovered. There are few data published on the incidence and the significance of secondary thrombocytosis. Many causes are known, but two major processes are involved: increased medullar production or abnormal control from spleen. It is believed to be a benign condition. The study of platelet dynamics could provide information about the course of the primary disease.*

Keywords: *thrombocytosis, inflammation, iron deficiency anemia, child*

Rezumat: *Trombocitoza secundară este definită ca şi creşterea numărului trombocitelor peste valoarea considerată fiziologică de 440.000/mm3, sau mai mare decât 2 deviaţii standard, secundar unei afecţiuni primare, cum ar fi infecţia sau anemia prin deficit de fier. Este observata la sugar şi copil mic, adesea descoperită întâmplător. În literatură sunt puţine informaţii legate de incidenţa şi semnificaţia clinică a trombocitozei secundare. Cauzele sunt multiple, două procese fundamentale sunt implicate: producerea exagerată la nivel medular si control deficitar la nivelul splinei. Trombocitoza secundară se presupune a fi o condiţie benignă. Studiul dinamicii trombocitare aduce informaţii importante corelate cu afecţiunea primară.*

Cuvinte cheie: *trombocitoză, inflamaţie, anemie feriprivă, copil*

Secondary thrombocytosis is defined as a growth of platelet number over 440.000/mm3 or more than 2 standard deviations, secondary to a primary disease like iron deficiency anemia or an infection. It is frequently observed in children, especially in infants and young children, often randomly discovered. There are few data published on the incidence and the significance of secondary thrombocytosis. Many causes are known, but two major processes are involved: increased medullar production or abnormal control from the spleen. It is believed to be a benign condition. The study of platelet dynamics could provide information about the course of the primary disease (1, 2, 3, 4, 5, 6).

The incidence of thrombocytosis is not known for sure. There are studies made by different authors, but by using different protocols, and for this reason the results could not be compared. There is no evidence that should suggest differences according to gender, ethny or origin country of the patient (15). According to a centralizing made by Sutor, a number of trombocytes (platelets) over 500.000/mm3 was identified in 3-13% of the patients hospitalized in the paediatric sections, whose trombocytes value in 0,5% of them was more than 800.000/mm3 (15).

A study made in a local paediatric hospital in order to identify the secondary thrombocytosis incidence and which was published in *Acta Haematologica* 2004 comprised 7.539 patients. By defining the secondary thrombocytosis as the increase of the number of trombocytes more than 500.000/mm3, an incidence of 6% (456 cases) was noticed. The incidence was dramatically changed according to age, thus thrombocytosis incidence in the newborn was of 12.5%, a top incidence in infants of one month old of 35.8%, while in the infants of 6-11 months old, the incidence reverted to the value of 12.9%. During adolescence, a percentage of only 0,6% was encountered. The most frequent causes described are: infection - 67.5%, Kawasaki disease - 9.4%, prematurity - 7.7% and sideropenic anemia – 6.4% (9,11). In order to establish the incidence and etiology of the secondary thrombocytosis, a study was made, which lasted for 12 months and comprised 7916 patients hospitalized in paediatrics clinics. Out of these, 36 (0.5%) had a number of trombocytes more than 800.000/mm3; 19 of them was of male gender and 17 were of female gender. An increased frequency was registered in infants and little children, the average age being of 13 month old. Regarding frequency, the causes considered primary affections which associate the secondary trombocytes are: bacterial infection, viral infection, sideropenic anemia, neoplazic affections after chemotherapy, after surgery status.

The causes of the secondary thrombocytosis are multiple and varied and are presented in table 1 (12). Regarding the secondary thrombocytosis associated to infection, the involvement of a mechanism induced by cytokines is suggested, making part of the normal

response of the organism to an infectious stimulus, suggesting trombocytes as an acute-phase reactant.

The dynamics of thrombocytosis is related to the evolution of the infectious process, the values reverting to normal in 1-2 weeks after healing (12).

In order to have a general view of the conditions that lead to the increase of trombocytes, the causes for a false thrombocytosis will also be presented (Table 2), as well as the primary thrombocytosis (Table 3) or the relative thrombocytosis (Table 4), important causes for the differential diagnosis (12). In paediatric pathology, thrombocytosis is rarely associated to a primary myeloproliferative disorder, such as the essential thrombocythemia or chronic myeloid leukaemia. These patients are predisposed to thrombotic or hemorrhagic complications, that is why it must be differentiated from the secondary thrombocytosis with a view to establish a proper therapeutic protocol (15).

Thrombocytosis secondary to an inflammation or to sideropenic anemia.

The exact mechanism of the secondary thrombocytosis is not fully known. Numerous studies were made in order to establish correlations between the primary affection and the increase of the thrombocytes number. One of the most frequent causes of secondary thrombocytosis in children is the viral or bacterial infection, most frequently the respiratory infection. The mechanism is known, interleukin 6 being the most important involved factor in TPO production at hepatic level. It may be presumed that thrombocytes are acute-phase reactants, because the thrombocytosis secondary to the infection makes part of the normal response of the organism regarding the inflammatory stimulus. After the remission of the inflammatory process, the serous level of the stimulating cytokines and the number of thrombocytes went back to normal, gradually. Their dynamics in relation with other reactants of acute phase is not exactly known. Regarding severe infections, such as bacterial meningitis, one of the thrombocytosis cause could be the "rebound" phenomenon, as a result of the initial thrombocytopenia due to the rapid consumption of thrombocytes. In October 2007, an infant of 11 month old was hospitalized in the ATI Clinic of Târgu Mureş, with the diagnosis of meningitis with MRSA, who presented thrombocytosis at the moment of hospitalization, with values above $9x10^5$/dl, values that 10 days after the beginning of the therapy remained over $9x10^5$/dl.

Evidence of a regulatory hormone of the thrombocytary production was mentioned even from 1950, when the increase of the number of thrombocytes was observed in the normal rats, which received plasma from the rats with bleeding due to thrombocytopenia. The term of thrombopoietin derives from erythropoiesis and its regulatory hormone. The c-Mpl receptor makes part of the receptors family for haematopoietic cytokines. The tests made with recombined proteins have proved that TPO is the main regulatory agent of thrombopoiesis, because its level is inversely proportioned with the megacariocitary weight and TPO infusion brings about an increase of thrombocytary production (7, 14)

Following the research, it has been noticed that the TPO level is inversely proportioned to the number of thrombocytes. The patients with aplastic anemia or the patients with thrombocytopenia secondary to the chemotherapic immunosuppression due to malignities had increased values of TPO.

A circumstance that does not obey the relation TPO/number of trombocytes is the inflammation, where the secondary thrombocytosis is accompanied by increased values of TPO. A major component of thrombopoietin regulation is represented by the collection and destruction mediated by receptors; receptors with great affinity for TPO being identified at thrombocytary level, which creates a self regulatory circuit (7, 9). An exception from the collection/destruction mechanism is represented by the physiologic response to the serious thrombocytopenia. The studies made indicate the fact that in normal conditions, the medullary stromal cells express less mARN for TPO, while the level of transcriptases for cytokines increases very much in the presence of thrombocytopenia. The precise mechanism of this circumstance is being researched. For example, a study shows that the proteins from the thrombocytary granules α, PDGF and FGF-2 increased the production level of TPO from the strom cells of the human medullars, while the platelet 4 factor and TGF-β recorded low levels for TPO of the same cellular type. Certain authors suggested the involvement of the hepatocytary growing factor (HGF) in the TPO production.

The way in which TPO production is adjusted within the context of the secondary, reactive thrombocytosis deviates from the known mechanism of TPO collection and destruction, because the serous level of the regulatory hormone is much higher than the prescribed one in relation with the thrombocytosis level. Inflammatory stimuli affect the TPO production through the acute-phase reacting agents, IL-6 increasing the TPO production at hepatic level. The effects observed in vitro were confirmed in vivo, the injection of IL-6 in mice and cancer patients led to the increase of mARN TPO, specific at the hepatic level and at the serous level of the TPO. The confirmation of the fact that TPO is the main factor of the reactive thrombocytosis within the inflammation was obtained by the administration of anti TPO serum and by the observance of the neutralization of the thrombopoietic effects induced by IL-6. (4, 6, 7, 9, 10).

Especially infants present reactive thrombocytosis within the context of the sideropenic anemia, especially with average values, but there were also cases with values higher than $1x10^6$. The mechanism by which this condition is developed is not known today, many theories existing in this respect. The studies made in the patients with sideropenic anemia and thrombocytosis compared with a witness batch proved that the only changed parameter was the erythropoietin in the case of

the patients with thrombocytosis, with values above the normal limit.

Thrombopoietin and cytokines, as well as IL-6, IL-11 had similar values with those of the witness batch. Thus, it has been reached the hypothesis according to which, due to the structural similarities between erythropoietin and thrombopoietin, the first would also relate to the thrombocytary receptors, c-Mpl, thus stimulating the thrombocytary production. In vitro studies made with recombined erythropoietin invalidated this.

Some authors studied the correlation between the serous level of iron, the number of leukocytes and thrombocytosis within the context of the sideropenic anemia in patients divided in two batches: with severe and mild anemia. Correlations between the number of thrombocytes and the serous level of iron were observed only in the case of the patients with mild anemia. Correlations between the number of thrombocytes and the number of leukocytes were observed in the case of the patients with severe anemia (1, 2, 3, 8, 13).

Table 1. Main causes for reactive thrombocytosis (12)

Inflammatory diseases	Infections	Acute
		Chronic (osteomyelitic hepatic tuberculosis)
	Rheumatoid arthritis	
	Inflammatory intestinal disease	
	Rheumatoid spondylitis	
	Sarcoidosis	
	Acute rheumatic fever	
	Kawasaki syndrome	
Hematologic disease	Iron deficiency	
	Chronic hemolytic anemia	
	Vitamin E deficiency	
	Acute bleeding	
	"Rebound" phenomenon after thrombocytopenia	
Medication induced	Vinca alkaloids	
	Corticosteroids	
Neoplazic diseases	Lymphoma	
	Neuroblastoma	
	Other tumours specific to childhood.	
Miscellaneous	After physical exercise	
	After surgical interventions	
	Caffey disease	

Table 2. Causes of false thrombocytosis (12).

False thrombocytosis	Microsferocytosid
	Pappenheimer bodies
	Leukocytary and erythrocytary fragments
	Bacteria

Table 3. Primary or autonomous thrombocytosis (12)

Myeloproliferative disorders	Essential thrombocythemia (familial, non-familial)
	Polycythemia vera
	Chronic myeloid leukaemia
	Agnogenic myeloid metaplasia
	Acute myeloid leukaemia
	Syndrome 5q
	Idiopatic sideroblastic anemia

Table 4. Causes of relative thrombocytosis (12)

Asplenia	Surgical
	Congenital
	Afunctional
Medication induced	Epinephrine

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