Immune thrombocytopenia in children and adults: what's the same, what's different?

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Patients are diagnosed with immune thrombocytopenia (ITP) when they suffer from isolated thrombocytopenia due to an unknown etiology.[1] Bleedings are found in approximately 2 out of 3 patients, typically petechiae, mucosal bleedings, menorrhagia and hematoma after minor trauma. While the abbreviation ITP has formerly been used for idiopathic thrombocytopenic purpura, it is now restricted to those patients with pathologies with an immunological cause. However, autoantibodies are only diagnosed in 50-60% of patients. ITP is, therefore, an "exclusion diagnosis," assuming that antibodies (circulating or platelet-bound) are not always detectable with standard diagnostic means, including Monoclonal Antibody Immobilization of Platelet Antigens (MAIPA). ITP is believed to be triggered by autoantibodies generated in response to bacterial or viral infections, vaccinations or drugs by a hapten mechanism. Some authors state that a diagnosis of ITP can also be applied as secondary to other (auto)immune diseases, including systemic lupus erythematodes, antiphospholipid syndrome, Evans syndrome, or AIDS.[1,2] Most antibodies are directed against the platelet surface receptors GPIIb/IIIa or GPIb/V/IX, although other receptors have also been targeted.[3] Several mechanisms for increased platelet turnover have been suggested: i) there is clear evidence that anti-platelet antibodies cause the decorated platelets to be recognized by the reticulo-endothelial system and degraded mainly in the spleen; ii) for some anti-

platelet antibodies the activation of the complement system has been shown to contribute to accelerated decrease in platelets by detection of the degradation components C1q or C4d in platelet-antibody complexes;[4] iii) in addition, *in vitro* stimulated T cells of some patients with ITP were able to trigger cytotoxic lysis of platelets by either $CD3^+CD8^+$ T cells or $CD56^+$ natural killer cells,[5] eventually in those patients in whom no circulating or platelet-bound antibodies can be detected. Taken together, these data provide evidence that both T- and B-cell dependent processes are involved in the pathogenesis of ITP. This has recently been shown in an elegant mouse model of ITP.[6]

In contrast, the influence of anti-platelet antibodies on thrombopoiesis by inhibiting megakaryocyte maturation in the bone marrow or platelet release across the endothelial barrier is still poorly characterized. It has long been known that antibodies present in the serum of ITP patients can bind to megakaryocytes[7] that share most of their surface receptors with platelets. Immunoglobulins present in the plasma of some patients inhibited or attenuated the differentiation of megakaryocytes from cord blood-derived $CD34^+$ hematopoietic stem cells.[8,9] In addition, megakaryocyte maturation and proplatelet formation is reduced in the presence of plasma of some ITP patients, implying that low platelet counts can also be due to an impaired production rate. However, the platelets that are released in ITP are much larger than in patients in whom thrombopoiesis is hampered due to a production defect, either congenital or in response to chemotherapy. Thus, the fraction of large, reticulated platelets or the "immature platelet fraction" has the power to distinguish ITP from production defects.[10] While normal or increased numbers of megakaryocytes are typically found within the bone marrow of patients, these cells are often smaller and show atypical features. So far, the role and degree of apoptosis in megakaryocytes has remained a matter of debate.[8,11]

Treatment of ITP involves corticosteroids, intraveneous immunoglobulins, anti-D, and rituximab (anti-CD20) that are used differentially during the acute and persistent/chronic phase of the disease (Table 1). Splenectomy is predominantly considered for refractory adult patients in the chronic phase.[1] Recently, the 2nd generation thrombomimics eltrombopag and romiplostim have received approval from both the US and the European agencies for treatment of this group of patients. First studies demonstrate that megakaryopoiesis and thrombopoiesis can further be stimulated in most of these patients and many long-term studies in adults with chronic form have been reported for each drug. However, it is worth mentioning that side effects, including bleeding, thrombotic events and myelofibrosis, have been recognized in a subset of patients in response to long-term application of either eltrombopag or romiplostim, respectively.[12] In the light of these data, the first published studies with thrombomimetics in children with chronic ITP should be considered with caution in order to avoid underestimating the risk of early reticulin deposition in the bone marrow.[13,14]

A substantial fraction of patients with ITP undergo spontaneous remission within three to six months after the initial diagnosis. These patients have formerly been referred to as "acute" while those with persistent low counts are referred to as "chronic". Recently, a new stratification has been suggested:[15] the term "acute" has now been attributed to those patients in whom remission occurs within three months after initial diagnosis and "persistent" when platelet counts normalize between three and 12 months. By definition, patients become "chronic" one year after diagnosis. Surprisingly, while about 80% of children undergo spontaneous remission, this rate is only 20% in adults. This finding implies two major findings in ITP. First, there are substantial differences in the occurrence of ITP in children and adults. Second, it is still not clear which factors might be predic-

Table 1. Key features of ITP in children and adults.

ITP	In children	In adults
Clinical	Extensive purpura Hemorrhagica (petechiae and hematoma), epistaxis, hematuria, bloody stools, metro- menorrhagia, conjunctival purpura, retinal bleeding, ICH (<0.5%)	
Prevalence	Prevalence of males Bleeding tendency: 90%	Prevalence of females Bleeding tendency: 70%
Diagnostic tools	Increased platelet size, reticulated platelets (Platelet-associated immunoglobulins, IPF) Platelet-associated immunoglobulins (PAIgs), MAIPA	
Spontaneous remission	approx. 80% within one year	Approx. 20-30% within one year
First-line treatment	"Wait and see" (if platelets are $>20\times10^9$/L) IvIG (if platelets are $<20\times10^9$/L and mucosal bleeding symptoms)	Corticosteroids IvIG anit-D
Other treatment options	Corticosteroids, anti D, Platelet concentrates and high dose corticosteroids in critical situations	Rituximab
Splenectomy in refractory chronic ITP	Should be avoided in children because of lifelong risk of OPSI syndrome Remission induction rate: 70-80%	Remission induction rate: approx. 65%
Thrombomimetics	First studies published	Approved for chronic ITP

tive for patients with ITP to undergo spontaneous remission compared to those who develop a chronic course. In this issue of Haematologica, both questions have been addressed.

Kühne and co-workers analyze the difference between adult and pediatric ITP.[16] They present a large study derived from prospective data collected by the Intercontinental Cooperative ITP Study Group (ICIS). The registry comprises data on 2,124 ITP patients at time of initial diagnosis among which 340 were adults. Kühne's work confirms that more male patients are found in the pediatric group while females were the majority in the adult group. However, despite this, there was far less difference in clinical and laboratory findings between the groups than expected. This includes the likelihood of overall bleeding when platelets were below 20×10^9/L, the initial platelet count and the percentage of patients who remained untreated. Obvious differences were found to be co-morbidities and the initial treatment: while IvIG was given in children, adults were more likely to have been treated with corticosteroids.

Polymorphisms in the Fcγ receptor IIA and IIIA have been identified that are over-represented in children with both acute or chronic ITP suggesting that carriers of this genetic constellation are more prone to develop ITP.[17] The second study presented in this issue provides exciting evidence that the Q63R polymorphism in the cannabinoid receptor CNR2 might be involved in the progression toward chronic ITP. Rossi *et al.* found that ITP patients homo- or heterozygous for the R allele of CNR2 have a markedly increased chance of becoming chronic.[18] The cannabinoid receptors are known to modulate the adaptive immune response, including the balance between T_{H1} and T_{H2} cells. Chronic ITP is known to have a balance towards the T_{H1} cell subset.[19] T cells from CNR2 63R homozygous individuals show a 2-fold reduction in inhibition of T-cell proliferation compared to Q-homozygous individuals. This polymorphism is more often found in patients with auto-immune diseases.[20] Therefore, it is feasible that the patients carrying at least one 63R allele might be prone to a chronic course of ITP. Further prospective studies will be required to address the prognostic value of this polymorphism.

Harald Schulze has studied biochemistry in Hannover and wrote his thesis on congenital and acquired thrombocytopenia. He received his postdoctoral training at the Dana-Farber Cancer Institute at Harvard Medical School, Boston. Since 2005, he has been heading an independent research group on megakaryocyte and platelet function and biology at the Charité Hospital. Gerhard Gaedicke became interested in hematology during his medical studies at the University of Hamburg. Later he joined Professor Kleihauer's group at the University of Ulm and was trained in pediatric hematology and oncology, including blood stem cell transplantation. Soon after Germany's reunification he became Full Professor of Pediatrics and Chairman of the Dept. of Pediatrics at the Charité University Medical Center, Berlin. His main interest besides hematolgy is the reform of the medical curriculum.

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