The name counts: the case of 'congenital amegakaryocytic thrombocytopenia'

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The name counts: the case of 'congenital amegakaryocytic thrombocytopenia'

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In this issue of Haematologica, Capaci et al describe a young Palestinian patient with inherited thrombocytopenia (IT) and severely reduced bone marrow megakaryocytes due to homozygous mutation (c. -323C>T) in the promoter region of the gene for thrombopoietin (THPO). This report adds further information on etiology and treatment of this recently identified form of amegakaryocytic thrombocytopenia and provides new insights into the mechanisms of THPO transcription.

Recent advances in the etiology of ITs revealed that mutations in several genes may be responsible for the reduction or absence of bone marrow megakaryocytes. The resulting diseases share the shortage of megakaryocytes but, due to their different etiologies, differ for the other associated clinical features, have different clinical course and prognosis, and require specific therapeutic approaches (Table 1). Thus, each gene causes a specific disease and it would be desirable for this to be highlighted by the name given to the illness. Unfortunately it is not always so, and disorders with different clinical features and causative genes have the same name. This has led to misunderstandings and uncertainties both in clinical practice and in scientific reports. The aim of this editorial is to illustrate briefly this matter and comment on the recent proposals for more effective names to be assigned to the ITs with reduced bone marrow megakaryocytes.

The first patient with congenital amegakaryocytic thrombocytopenia has been described in 1929 by Greenwald and Sherman. Seventy years later a series of papers concluded that many, but not all patients with this clinical picture had biallelic mutations in the gene MPL encoding the THPO receptor. This form of inherited thrombocytopenia received the name of Congenital AMegakaryocytic Thrombocytopenia (CAMT). Large case series revealed that the prognosis of affected patients is very poor, because all patients are destined to die either from hemorrhage or from the severe bone marrow aplasia that always arises in the first years of life. The only hope of reaching adulthood is offered by hemopoietic stem cell transplantation (HSCT).

The name CAMT is used also for the recently discovered IT caused by biallelic THPO mutations. Similarly to patients with CAMT due to MPL mutations, also subjects with mutated THPO present with congenital amegakaryocytic thrombocytopenia and evolve towards bone marrow aplasia. However, they do not benefit from HSCT because the scarcity of megakaryocytes does not result from a defect of progenitor cells, but is instead caused by the inability of liver cells to produce THPO (as evidenced by the fact that serum THPO levels are low in this condition while they are elevated in all other forms of congenital amegakaryocytic thrombocytopenia). As a matter of fact, the outcome of HSCT was poor due to failure of engraftment in all patients with THPO mutations who received this treatment. Instead, and not surprisingly, the THPO-receptor agonists romiplostim or eltrombopag have proven very effective in quickly increasing platelet count and also making pancytopenia disappear in case it has already established. Another difference that may be relevant for the diagnostic process and genetic counselling is the mode of
transmission, in that some subjects with monoallelic \textit{THPO} mutations have mild thrombocytopenia, while those with monoallelic \textit{MPL} mutations always have normal phenotype. Based on these considerations, Germeshausen and Ballmaier proposed that names of the affected genes are added as suffixes to CAMT to emphasize that CAMT from \textit{MPL} or \textit{THPO} mutations differs in some relevant respects.\textsuperscript{2} The authors of the article that prompted this editorial have adhered to this recommendation and use the terms CAMT-MPL and CAMT-THPO in their paper.

Besides \textit{MPL} and \textit{THPO}, also the genes \textit{HOXA11}\textsuperscript{9} and \textit{MECOM}\textsuperscript{10} can be causative of congenital thrombocytopenia due megakaryocyte shortage and propensity to bone marrow aplasia, in this case variably associated with radio-ulnar synostosis and/or other malformations. If patients develop signs of bone marrow failure, there is an indication for HSCT. Regardless of the affected gene, the names RadioUlnar Synostosis with Amegakaryocytic Thrombocytopenia (RUSAT) or Congenital amegakaryocytic Thrombocytopenia with RadioUlnar Synostosis (CRUS) have been used for both conditions. The main difference between the disorders caused by \textit{HOXA11} and \textit{MECOM} is that the very few patients with \textit{HOXA11} mutations reported so far all had proximal radioulnar synostosis, but only some of them had the hematological phenotype. At the opposite, all subjects with \textit{MECOM} mutations have the hematological phenotype but some of them do not present radio-ulnar synostosis and are therefore at risk of misdiagnosis with CAMT-THPO or CAMT-MPL. Moreover, the spectrum of possible malformations caused by \textit{MECOM} is wider than that of \textit{HOXA11}. Based on these differences, the names CTRUS-HOXA11 and \textit{MECOM}-Associated Syndrome (\textit{MECOM-AS}) have been proposed by Germeshausen et al.\textsuperscript{11}

Thrombocytopenia-absent radius syndrome (TAR) is a further genetic disorder characterized by congenital thrombocytopenia with reduced bone marrow megakaryocytes, in this case always associated with bilateral radial aplasia and sometimes with other congenital defects. It is caused by compound heterozygosity for a null mutation involving the \textit{RBM8A} gene and 1 of 2 low-frequency noncoding single-nucleotide polymorphisms in \textit{RBM8A} on the other.\textsuperscript{12} In contrast to the disorders with amegakaryocytic thrombocytopenia mentioned above, this form does never progress to bone marrow failure, but instead tends to improve spontaneously because platelet count usually begins to rise after the first year of life and sometimes even normalizes. HSCT is therefore not indicated and the therapy is supportive in anticipation of the spontaneous reduction of thrombocytopenia. Of note, one patient with TAR needing surgery had her platelet count normalized by the \textit{THPO} receptor agonist romiplostim.\textsuperscript{13} Recognizing that congenital amegakaryocytic thrombocytopenia is due to TAR has therefore important practical consequences, but fortunately diagnosis is easy because the association of congenital thrombocytopenia with bilateral radial aplasia is pathognomonic of this condition. The name TAR is therefore appropriate because it well describes this disease with very peculiar characteristics.

The case of congenital amegakaryocytic thrombocytopenias exemplifies well how the advancement of knowledge about hereditary diseases has increased the number of known causative genes and has revealed that what we once considered single diseases actually consist of multiple disorders with clinically relevant differences. Although trying to change the name of long-known diseases risks creating more harm than good, I believe that Germeshausen and Ballmaier’s proposal for including the causative gene in the name of some congenital amegakaryocytic thrombocytopenias is to be accepted because it tidies up a complex matter that in the past has been subject to misunderstandings. The observation that the name of the many new forms of inherited thrombocytopenia discovered in recent years makes mention of the defective gene testifies that this idea is shared by those who deal with these diseases. The time in which the name of ITs
was that of whoever discovered them or derived from one of the features of the first described patients is ending. It is possible that other diseases identified long ago will have their names changed in the future.

References

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Table 1. Essential features of the five inherited thrombocytopenias presenting with congenital amegakaryocytic thrombocytopenia. New names have been recently proposed for four of these disorders.

<table>
<thead>
<tr>
<th>Causative gene</th>
<th>MPL</th>
<th>THPO</th>
<th>HOXA11</th>
<th>MECOM</th>
<th>RBM8A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current name of the disorder(s)</td>
<td>Congenital amegakaryocytic thrombocytopenia (CAMT)</td>
<td>Congenital amegakaryocytic thrombocytopenia with radio ulnar synostosis (CTRUS)</td>
<td>Thrombocytopenia absent radius syndrome (TAR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New proposed name</td>
<td>CAMT-MPL</td>
<td>CAMT-THPO</td>
<td>CTRUS-HOXA11</td>
<td>MECOM-associated syndrome (MECOM/AS)</td>
<td>TAR</td>
</tr>
<tr>
<td>Inheritance</td>
<td>AR</td>
<td>AR</td>
<td>AD</td>
<td>AD</td>
<td>AR</td>
</tr>
<tr>
<td>Reduced-absent megakaryocytes at birth</td>
<td>all patients</td>
<td>all patients</td>
<td>all patients</td>
<td>all patients</td>
<td>all patients</td>
</tr>
<tr>
<td>Progression to bone marrow failure</td>
<td>all patients</td>
<td>all patients</td>
<td>most patients</td>
<td>all patients*</td>
<td>no, platelet count instead rises over time</td>
</tr>
<tr>
<td>Radio-ulnar synostosis</td>
<td>no</td>
<td>no</td>
<td>all patients</td>
<td>most patients</td>
<td>no</td>
</tr>
<tr>
<td>Bilateral radial aplasia</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Other defects</td>
<td>no*</td>
<td>no</td>
<td>some patients</td>
<td>some patients</td>
<td>many patients</td>
</tr>
<tr>
<td>Serum thrombopoietin</td>
<td>high</td>
<td>low</td>
<td>high</td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td>Treatment</td>
<td>HSCT</td>
<td>THPO-RA (no HSCT!)</td>
<td>HSCT</td>
<td>HSCT</td>
<td>supportive</td>
</tr>
</tbody>
</table>

*Spontaneous amelioration of pancytopenia reported in one patient; °central nervous system defects have been reported, but they were probably secondary to brain hemorrhages during intrauterine life; AR: autosomal recessive; AD: autosomal dominant; HSCT: hematopoietic stem cell transplantation; THPO-RA: thrombopoietin receptor agonists
Figure 1. The spectrum of ITs with congenital amegakaryocytic thrombocytopenia. Mutations of five different genes cause congenital amegakaryocytic thrombocytopenia in the context of clinical phenotypes peculiar to each etiopathogenetic mechanism. The only three names in use today for these diseases are therefore unable to properly describe the five diseases, and new names have been proposed that include the defective gene to emphasize that etiological differences result in clinically relevant differences.
Congenital amegakaryocytic thrombocytopenia with radio-ulnar synostosis (CTRUS)

Congenital amegakaryocytic thrombocytopenia (CAMT)

Thrombocytopenia absent radius syndrome (TAR)