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REVIEW

Congenital Amegakaryocytic Thrombocytopenia

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Congenital amegakaryocytic thrombocytopenia (CAMT) is clinically characterized by thrombocytopenia presenting at birth in a child without congenital or skeletal malformations, reduced or absent bone marrow megakaryocytes, and eventual progression to bone marrow failure. Molecular studies in most cases confirm homozygous or compound heterozygous mutations in the thrombopoietin receptor c-Mpl. In addition to the clinical importance of recognizing this disorder, characterization of mutations identified in patients with CAMT has led to insights into thrombopoietin receptor structure and function. This review will summarize the diagnosis, pathophysiology, and management of CAMT. Pediatr Blood Cancer 2011;57:199–203.

Key words: c-Mpl; inherited thrombocytopenia; neonatal thrombocytopenia

INTRODUCTION

Thrombocytopenia is a relatively common clinical problem in hospitalized neonates, and it can be difficult to distinguish infants with rare congenital thrombocytopenias from those with acquired disorders. The majority of neonatal thrombocytopenia is infectious or immune in etiology. Congenital disorders that present with severe thrombocytopenia in the newborn period include thrombocytopenia with absent radii (TAR, MIM #274000), amegakaryocytic thrombocytopenia with radioulnar synostosis (ATRUS, MIM #605432), Paris Trousseau syndrome (MIM #188025), and congenital amegakaryocytic thrombocytopenia (CAMT, MIM #604498). CAMT is an autosomal recessive disorder due to mutations in the thrombopoietin (TPO) receptor c-Mpl [1]. Although CAMT can generally be distinguished clinically from TAR, ATRUS, and Paris Trousseau syndrome by the absence of other congenital or skeletal abnormalities, genetic testing has made it easier to definitively diagnose this disorder in children with isolated thrombocytopenia. In addition, characterization of different mutations identified in patients with CAMT has led to insights into c-Mpl structure and function that have contributed to our overall understanding of thrombopoietin signaling.

PRESENTATION AND DIFFERENTIAL DIAGNOSIS

CAMT is an autosomal recessive disorder that presents at birth with severe (platelets $<50{,}000/\mu l$) thrombocytopenia. Mean platelet counts at diagnosis are approximately $20{,}000/\mu l$, and when reviewed on peripheral blood smears, platelets are of normal size and granularity [2]. Importantly, phenotypic findings in CAMT are usually limited to those related to thrombocytopenia, including cutaneous and intracranial hemorrhage before or after birth. King and co-workers [2] described several patients with clinical features of CAMT that also exhibited growth or developmental delay, strabismus or central nervous system abnormalities including cerebellar malformations and cortical dysplasia. The relationship of these findings to the pathophysiology of the disorder is unclear; however, c-Mpl expression has been detected in neurons in various locations within the brain [3]. Nevertheless, as no specific congenital defects are characteristic of CAMT, in general consideration should be given to an alternative syndrome if such malformations are present.

CAMT is a rare cause of thrombocytopenia in the newborn period; much more frequent etiologies include prenatal factors (pre-eclampsia, placental insufficiency, intrauterine growth retardation), anoxic insult, infection (including TORCH agents and sepsis), or maternal transfer of platelet allo- or autoantibodies. The timing of onset of thrombocytopenia, its severity, as well as clinical history and maternal platelet counts are often helpful in identifying underlying factors contributing to neonatal thrombocytopenia [4]. Neonatal alloimmune thrombocytopenia (NAIT) is an especially important cause of severe thrombocytopenia in an otherwise well-appearing newborn that must be differentiated from CAMT. NAIT is more common than CAMT (1:1,000–1:2,000 live births [5,6] compared to less than 100 reported cases of CAMT). Establishing the correct diagnosis has important implications for management the infant as well as counseling regarding subsequent pregnancies, and therefore it is important to consider NAIT in any newborn whose platelet counts are $<50{,}000/\mu l$ when maternal platelets are normal [7]. Genotyping can establish if there is incompatibility between maternal and paternal platelet antigens that would predispose to alloimmunization, and serologic assays using patient or maternal serum may detect platelet-specific alloantibodies [7–9]. Bone marrow aspiration is not usually required to diagnose NAIT but if performed typically shows normal cellularity with normal to increased megakaryocytes. Following birth the maternally derived platelet alloantibody diminishes and after the first month of life the expectation is that platelet counts will improve. In a child suspected to have NAIT, if thrombocytopenia does not resolve after 3 months, alternative diagnoses such as CAMT should be explored [10,11]. Furthermore, clinicians should maintain a high index of suspicion for CAMT in infants in whom thrombocytopenia transiently improves and then recurs [12].

If a bone marrow aspiration is performed in the newborn period, infants with CAMT classically have a reduction or absence of megakaryocytes in an otherwise normocellular marrow [2]. The megakaryocytes that are present may look small or immature. However, in some cases, marrows studied early in the course of the disease have only subtle megakaryocyte

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abnormalities and serial marrows may be required to clarify the diagnosis [10,11]. Later in the course of the disease patients will have hypocellular marrows with decreased progenitors in all lineages, and they may be difficult to distinguish from patients with other forms of aplastic anemia [13].

Measurement of plasma TPO levels is a useful diagnostic assay in the evaluation of congenital thrombocytopenia; however, it is not widely available. TPO is produced at a constant rate by the liver and removed from the circulation by receptor-mediated uptake and destruction [14–16]. As the c-Mpl expressed on megakaryocytes and platelets represents the majority of the receptor available to bind to TPO [17], when megakaryocyte and platelet production are low, plasma TPO levels rise. In addition to severely reduced thrombopoiesis, in CAMT the megakaryocytes and platelets that are present do not express functional c-Mpl. Therefore, plasma TPO levels in children with CAMT are very high, often 10-fold or more above controls [18]. By comparison, when thrombocytopenia is due to platelet destruction such as in patients with immune thrombocytopenia, TPO levels are normal or only modestly elevated [19,20].

In children in whom the diagnosis is suspected based on clinical findings, CAMT can be confirmed by finding homozygous or compound heterozygous mutations in the TPO receptor c-Mpl [1,18]. Mutations have been found throughout c-Mpl, including nonsense, missense and splicing mutations, and therefore testing should include the entire coding region and intron/exon boundaries. The most common location for mutations is within exons 2 and 3, encoding the first cytokine receptor homology domain; mutations within this region that create a frame shift or premature stop codon disrupt the entire intracellular domain of the receptor [1,10,12,13,21–25]. Such mutations can be predicted to result in a complete loss of receptor function. The effects of mutations that create amino acid substitutions or potentially interfere with splicing are more difficult to predict (see below), but in the context of a patient with clinical features suggesting CAMT are likely to be causative. Importantly, one commonly observed substitution, methionine for valine at amino acid 114, has been shown to be a polymorphism that is not associated with disease [13]. Clinically certified mutation analysis of c-Mpl can now be obtained at GeneDx (Gaithersburg, MD) and Prevention Genetics (Marshfield, Wisconsin).

Although mutations in c-Mpl provide a molecular definition for CAMT, rare children fulfill clinical criteria for the disorder yet lack detectable c-Mpl mutations. One possibility is that these children have mutations in upstream, non-coding gene sequences that regulate c-Mpl expression. Most clinically available gene sequencing only interrogates coding exons and intron/exon boundaries and could miss such upstream mutations. Alternatively, mutations in genes besides c-Mpl could interfere with TPO signaling and lead to CAMT. For example, mice lacking TPO phenocopy those without c-Mpl [26]. To date however, mutations in genes other than c-Mpl have not been identified in children with CAMT.

PATHOPHYSIOLOGY

Platelets are produced by bone marrow megakaryocytes, which in turn are derived from the hematopoietic stem cell (HSC). Although other cytokines and factors contribute to the growth and maturation of megakaryocytes, TPO is the primary regulator of platelet production [27–29]. Proof of the importance of TPO signaling for megakaryocyte development comes from mouse models. In mice, the deletion of TPO or its receptor c-Mpl results in a severe reduction in megakaryocytes and peripheral thrombocytopenia [29,30]. In addition, although they do not develop anemia or neutropenia, mice that lack c-Mpl have approximately 10% of normal HSC numbers, and marrow progenitors for all of the hematopoietic lineages are reduced [26,29,31]. This finding provided an important insight that TPO signaling is important not just for platelets but also for the maintenance of the HSC. Subsequent studies confirmed that TPO promotes quiescence in long-term HSCs [32–34] and expansion of post-natal HSCs [32]. TPO was also shown to enhance the expression and function of VEGF, HoxB4, and HoxA9 in hematopoietic progenitors, providing potential mechanisms by which TPO signaling could be linked to pathways known to promote HSC growth and survival [35–37]. But the most incontrovertible evidence that TPO is required for the maintenance of the HSC is found in the clinical course of children with CAMT and c-Mpl mutations, who nearly all go on to develop trilineage bone marrow failure within the first decade of life [1,18].

Further studies have sought to clarify the relationship between individual c-Mpl mutations and the clinical course of the disease, particularly the timing of onset of marrow failure. Ballmaier and co-workers [2,12] described two classes of c-Mpl mutation, types I and II. Type I mutations often create a premature stop codon or frame shift that completely eliminates receptor signaling through ablation of all or most of the intracellular domain. This type of mutation is generally associated with early progression to bone marrow failure [12]. Alternatively, children who inherit mutations that cause splicing defects or amino acid substitutions (type II mutations) may have a less aggressive course with a relatively delayed onset of marrow failure, possibly resulting from residual receptor function [12]. As the effects of

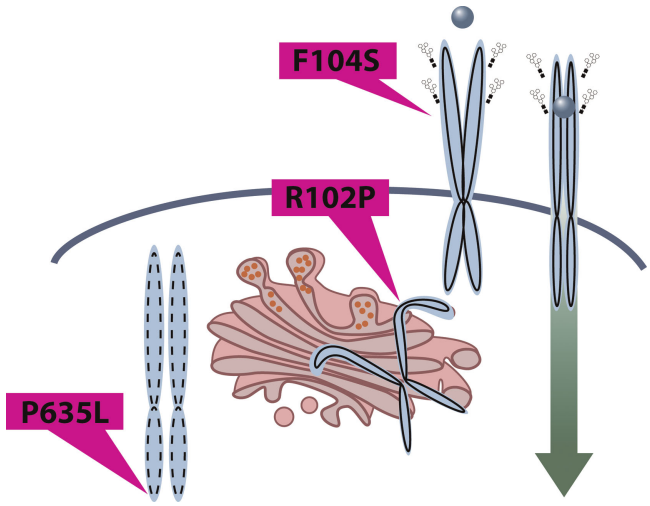

Fig. 1. c-Mpl mutations alter receptor function in a variety of ways. Whereas the wild-type receptor (rightmost in figure) is glycosylated and expressed on the cell surface where it can productively interact with TPO, F104S c-Mpl is expressed on the surface but unable to bind TPO. R102P c-Mpl is poorly glycosylated and poorly expressed on the cell surface. P635L is unstable, but if its degradation is inhibited it can go to the membrane and signal. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

type II mutations on receptor structure and function are difficult to predict, they have been investigated using in vitro models. For example, Drachman et al. studied a splicing mutation identified in an 11-year-old female with thrombocytopenia and a hypocellular marrow. Expression of the mutation as a minigene in a cell line model indicated that production of the correctly spliced c-Mpl transcript was reduced but not eliminated, potentially explaining the relatively late onset of marrow failure and delayed diagnosis of CAMT in this family [13]. Cell line models have also been utilized to evaluate type II mutations creating amino acid substitutions in patients with CAMT (Fig. 1). The most common of these mutations results in the substitution of proline for arginine at residue 102 (R102P) in the extracellular domain. When expressed in cell lines, R102P c-Mpl was not glycosylated and did not reach the cell surface, and thus was not able to interact with TPO [11]. A similar pattern of receptor hypoglycosylation was observed for the mutations R257C, R257L, and W154R c-Mpl [38]. In contrast, a mutation in which serine replaces phenylalanine at reside 104 (F104S) retained normal expression of the mutant c-Mpl on the cell surface. However, likely due to the loss of stabilizing hydrogen bonds, F104S c-Mpl is unable to bind TPO and does not signal in response to the cytokine. Intriguingly, because the receptor is otherwise intact, this signaling defect can be circumvented by stimulating cells with a TPO receptor agonist that binds to an alternative site within the intracellular domain of c-Mpl [38]. A third mechanism of receptor dysfunction occurs with the mutation P635L, resulting in the substitution of the terminal proline of the receptor with leucine. Tijssen et al. [39] reported that P635L c-Mpl is poorly expressed in K562 cells. We have recently extended these findings to confirm that the stability of P635L c-Mpl is greatly reduced compared to the wild-type receptor, but the addition of a proteasome inhibitor results in improved surface expression of the mutant receptor and partially rescues its function (Zhang et al. manuscript in preparation). The mechanisms by which other substitutions interfere with signaling are not always clear and further study using structural or cell line models may lead to new insights into receptor structure and processing.

CLINICAL COURSE AND MANAGEMENT

As mentioned above, thrombocytopenia in patients with CAMT can have a variable clinical course [2]. Whereas infants with type I receptor mutations generally remain thrombocytopenic and have a rapid progression to trilineage bone marrow failure (mean onset 1 year 11 months of age), infants with type II mutations may show transient modest improvement of platelet counts during the first year of life and have a delayed onset of marrow failure (mean onset 5 years of age) [2]. Nevertheless, with rare exception patients with c-Mpl mutations develop aplastic anemia, and CAMT is regarded as one of the inherited bone marrow failure syndromes. Some analyses have also suggested that patients with CAMT are at increased risk for the development of myelodysplasia and acute myeloid leukemia [40]. Although leukemia has been reported in patients with CAMT, small numbers make it difficult to determine the magnitude of this risk in relationship to other types of bone marrow failure such as Fanconi Anemia.

Supportive care in patients with CAMT consists primarily of platelet transfusions and adjunctive therapies such as fibrinolytic inhibitors to manage bleeding symptoms, as well as red cell transfusions and antibiotics once anemia and neutropenia develop. The use of alternative cytokines to stimulate thrombopoiesis has shown some efficacy in mouse models [41,42] but clinical use is limited by toxicity. Given the lack of functional c-Mpl in hematopoietic stem cells and megakaryocytic progenitors it is unlikely that TPO receptor agonists will be therapeutically useful in the majority of patients with this disease [11,39], except possibly in rare cases where the mutation interferes specifically with TPO binding [38]. Gene therapy has been proposed as a strategy to correct the stem cell defect by repairing the mutant c-Mpl [43,44]; however, concerns regarding potential leukemogenicity of this approach remain [45].

Currently, the only definitive treatment available for the long-term management of patients with CAMT is HSC transplantation. HLA typing for the patient and siblings should be obtained at the time of diagnosis to direct management decisions. Transplantation with a matched sibling donor is the treatment of choice, if available [2,46,47]. Siblings who are heterozygous carriers of the c-Mpl mutation have been used successfully as stem cell donors [23]. Historically, outcomes have been less favorable for patients without a matched sibling donor, due to problems with delayed engraftment, rejection, GVHD and regimen related toxicity [2,48,49]. However, more recent studies suggest that unrelated donor transplants are viable options in CAMT [50]. Although the numbers of patients are very small, haploidentical parents have also been used with some success [2,46]. The optimal timing of transplant is not known but has been suggested to be before pancytopenia develops, thus limiting transfusion exposures and risk for infections that could compromise transplant outcome. In the review by King and co-workers [2], 15 of 20 patients received transplants at a median age of 38 months (range 7–89 months). Further studies are needed to optimize donor selection and conditioning for patients with CAMT, particularly those who lack a matched sibling donor.

SUMMARY

Thrombocytopenia in the newborn period can have diverse etiologies but among them it is important to consider congenital disorders such as CAMT. Making the correct diagnosis is critical for optimal management as well as appropriate counseling for the family. Genetic testing is now readily available, and therefore children suspected to have CAMT should be screened for mutations in c-Mpl. Identification of c-Mpl mutations in affected patients is useful for confirmation of the diagnosis and may lead to further insights into TPO signaling. Currently, HSC transplant with the best available donor is the treatment of choice for children with CAMT.

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