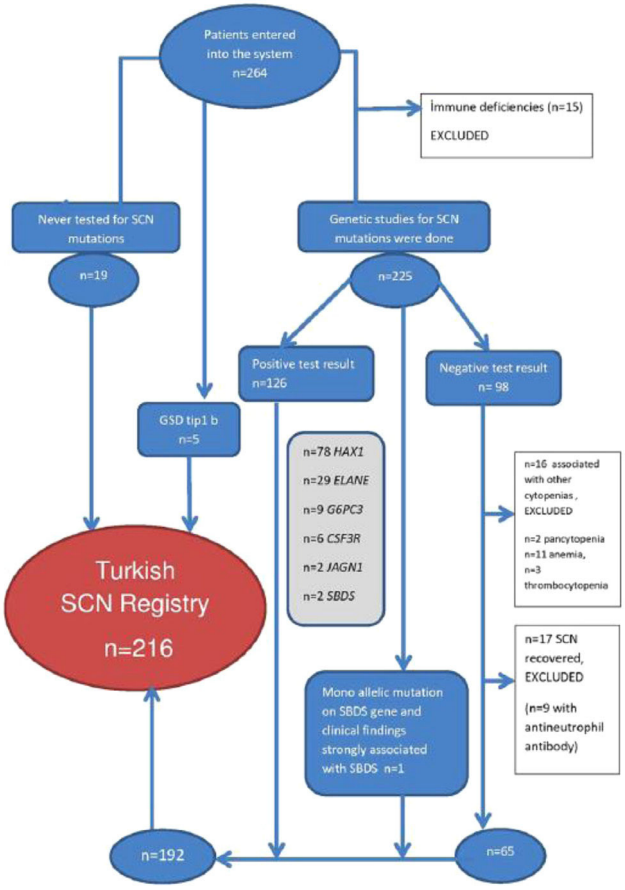
W44X. There were 6 patients who had a HAX1 mutation other than c.130-131 pW44X point mutation. Four had novel mutations. The novel mutations were detected in 7 ELANE patients. Interestingly 2 out of 4 patients with CSF3R mutation and 4 out of 9 patients with G6PC3 had a novel mutation.

Granulocyte colony-stimulating factor treatment was given to 174 patients (80.6%). Two patients died with infectious complications, and five patients developed myelodysplastic syndrome/acute myeloblastic leukemia (Table 2). The mean (± mean standard error) follow-up period was 129.7 ± 76.3 months, and overall survival was 96.8% (CI, 94.4-99.1%) at the age of 15 years.

In Turkey, mutation analysis should be started with HAX1, and if this is negative, ELANE and G6PC3 should be checked. Because of the very high percentage of consanguineous marriage, rare mutations should be tested in patients with a negative mutation screen.



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Sp 10

Hereditary macrothrombocyte disorders

Zühre Kaya

Hereditary macrothrombocyte disorders as known inherited macrothrombocytopenia (IMTP) are gaining greater recognition through advanced genetic and molecular studies. It is a heterogenous group of rare bleeding disorders characterized by abnormally giant platelets, thrombocytopenia, mild to moderate bleeding phenotypes, and/or positive family history and/or syndromic findings. The main characteristic features of macrothrombocytopenia are reduced platelet count (<150,000/μL) and significantly enlarged platelets (mean platelet volume (MPV) >12fL). Up to now, more than 30 genes linked to IMTP have been identified in nearly half of the patients with syndromic and non-syndromic IMTP. All inheritance patterns, including autosomal dominant, recessive, and sex-linked, have been described; however, nearly 50% of affected patients have unidentified genetic mutations or molecular abnormalities. The early and late stages of megakaryopoiesis and subsequent proplatelet formation and functional platelet are regulated by a large number of genes. Defects in these genes result in the dysfunction of several steps in megakaryopoiesis, proplatelet formation, and mature platelet. Many patients with non-syndromic IMTP are either asymptomatic or have minor bleeding manifestations and, detected incidentally with platelet count and morphology evaluation; however, patients with syndromic IMTP may be early diagnosed by specific clinical findings in addition to macrothrombocytopenia. Physicians should suspect IMTP if the following clinical and laboratory findings are present:

a Hearing loss, cataracts, impaired renal function, elevated hepatic enzymes and Döhle-like bodies in neutrophil for non-muscle myosin heavy chain (MYH)-9 related disease,
b Splenomegaly, bone marrow fibrosis, pale platelet and elevated serum levels of vitamin B12 for gray platelet syndrome,
c Cardiac abnormalities, dysmorphic face, digital abnormalities and mental retardation for Paris Trousseau thrombocytopenia/Jacobsen syndrome,
d Craniofacial defects, cardiac abnormalities, mental retardation, hypotonia, thymic aplasia, immune deficiency for DiGeorge syndrome/Velocardiofacial syndrome,
e Xanthomas, premature atherosclerosis, arthritis, hemolytic anemia with stomatocytes, elevated plasma phytosterols for sitosterolemia.

No definitive guidelines are available for managing asymptomatic or mildly symptomatic patients with IMTP; however, platelet transfusion, antifibrinolytic therapy, and recombinant factor VIIa are usually recommended for those with severe bleeding manifestations or prior to surgery. Recently, it has been reported that thrombopoietin-receptor agonists can be used in some patients with MYH9 related disorders. The International Society of Thrombosis and Haemostasis' scientific subcommittee on platelet physiology has published guidelines for diagnosing IMTP. In this approach, personal and family history, and physical examination are the key, followed by i) investigation of platelet count and morphology, ii) evaluation of platelet function by light transmission aggregometry, and iii) a panel of tests to assess granule contents and platelet surface markers by electron microscopy and flow cytometry studies. Further, next-generation sequencing has greatly expanded the molecular repertoire of IMTP, thus enabling the identification of new disorders.

Laboratory findings[2,5,14,15]

a Abnormal complete blood count parameters, including platelet count and MPV may be detected incidentally in many cases. Platelet count below 150,000/μL and significantly increased platelet size (MPV >12 fL) are pathognomonic findings.
b Abnormal platelet morphology may be observed in peripheral blood smear. In patients with IMTP, on average, 20% of platelets are large (>4μm diameter), and 12% are giant (>8 μm diameter) (normal platelets size are between 1.5 μm and 3 μm in diameter). As well, *vacuolated platelets* for GATA1 related disease, *giant platelets* for MYH9 related disease, biallelic Bernard Soulier syndrome (BSS) (GP1bα, GP1bβ and GP9-moderate to severe phenotype), GPS, FLNA related and TUBB1 related disease, *large platelet* for monoallelic BSS (GP1bα-mild phenotype), Paris-Trousseau/ Jacobsen syndrome, GATA1 related-, ITGA2B- and ITGB3 related-disorders are diagnostic signs in peripheral blood smear.
c Abnormal platelet function by light transmission aggregometry may be observed in patients with BSS (*e.g.*, Ristosetin induced platelet aggregation response is absent).
d Immunofluorescence testing with antibody against nonmuscle myosin heavy chain reveals a spotty abnormal distribution of these molecules in patients with MYH9 disorders.
e Flow cytometry reveals lack of GP1bα, GP1bβ and GP IX receptor in patients with BSS.
f Two-dimensional sodium dodecyl sulfate-polyacrylamide gel electrophoresis of the surface radio iodinated platelet glycoproteins results show the absence of GPIb which identifies BSS.
g Electron microscopy reveals abnormal ultrastructure of platelets (*e.g.*, lack of alpha granules and inclusions in MYH9 disorders, giant fused alpha granules in Paris-Trousseau syndrome).
h The next-generation sequencing technology has enabled comprehensive genetic testing using broad diagnostic panels for IMTP related disorders. Recent studies using whole-exome sequencing and whole-genome sequencing have greatly contributed to the early recognition of IMTP related genes and the detection of pathogenic variants within these genes.

v. Treatment: No definitive guidelines are available for managing asymptomatic or mildly symptomatic patients with IMTP; however, platelet transfusion, antifibrinolytic therapy, and recombinant FVIIa are usually recommended for those with severe bleeding manifestations.[5,15] Recently, it has been reported that TPO-receptor agonists can be used in some patients with MYH9 related disorders.[5]

Conclusion: The International Society of Thrombosis and Haemostasis' scientific subcommittee on platelet physiology has published guidelines for diagnosing IMTP. In this approach, personal and family history, and physical examination are the key, followed by *i*) investigation of platelet count and morphology, *ii*) evaluation of platelet function by light transmission aggregometry, and *iii*) a panel of tests to assess granule contents and platelet surface markers by electron microscopy and flow cytometry studies. Further, next-generation sequencing has greatly expanded the molecular repertoire of IMTP, thus enabling the identification of new disorders.

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Sp 11

Treatment of sickle cell in 2021

Salam Alkindi

Sickle cell disease (SCD) is an inherited disorder prevalent in many areas of the world including Africa, Middle East and parts of India. It is characterized by repetitive episodes of vaso- occlusive (VOC) process leading to recurrent painful episodes, hemolytic anemia, and predisposition to infection. Sickle cell manifestations varies and it includes VOC leading to recurrent painful episodes, or organ specific complications such as acute chest syndrome, stroke, splenic sequestration, and many skeletal complications. Although the prognosis of patients with SCD has improved, due to introduction of vaccination, use of antibiotics prophylaxis and blood transfusions, however still patients are dying prematurely. Better understanding of pathophysiology of the disease as well as worldwide interest in the disease has allowed more progress on preventing these complications and development of more focused pharmacological therapies. Hemoglobin polymerization is a primary triggering event in the pathophysiology of the disease, leading to the sickling process, this usually ignite an inflammatory process/ tissue ischemia and increased adhesions. This understanding of the pathophysiology has allowed scientist to develop drugs (three FDA approved within 2 years) that interfere with these processes such as Voxelotor & Hydroxyurea (interfere with polymerization), L-glutamine and Omega 3 (interfere with inflammatory process and oxidative stress) and Crizanluzimab and Tinzaparin (works by inhibiting adhesion molecules). The availability of these therapeutic interventions will allow patients and physicians the freedom to have patient specific therapeutic interventions including development of combinations protocols. SCD is very complex and this meant that drug with multi-faceted action such as Hydroxyurea will remain with us for some time. Further progress also made in the area of bone marrow transplant (including alternative donor pool) and gene therapy /gene editing.

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