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## Gray platelet syndrome, more than just a bleeding disorder

### Síndrome de plaquetas grises, algo más que un trastorno hemorrágico

*Dear Editor:*

Gray platelet syndrome (GPS) rare inherited bleeding disorder characterized by macrothrombocytopaenia and reduction of α-granules in platelets and in megakaryocytes, which results in the presence hypogranular platelets with a grey appearance in blood smears. Affected patients present with bleeding diathesis, progressive myelofibrosis and splenomegaly. The exact prevalence of GPS is unknown, and approximately 60 cases have been reported worldwide to date.[1]

The syndrome is caused by a homozygous or compound heterozygous variant in the *NBEAL2* (3p21) gene that encodes the neurobeachin-like 2 protein (NBEAL2), a member of a family of proteins containing Beige and Chediak-Higashi (BEACH) domains believed to be involved in vesicle trafficking and critical for the development of α granules.[2]

We describe the case of a boy aged 22 months referred for assessment of mild thrombocytopaenia detected in a routine blood test. The patient was in follow-up in the otorhinolaryngology department due to enlargement of the adenoids and tonsils that caused snoring and sleep apnoea/hypopnoea. The had been born to term following in vitro fertilization (egg donation).

The salient findings of the physical examination were adenoid facies and mouth breathing, snoring and breathing difficulty when awake, obstructive tonsillar hypertrophy, hepatomegaly with a liver diameter of 3 cm, splenomegaly with a spleen diameter of 4 cm and bilateral cervical lymphadenopathy.

Due to the significant impairment resulting from the obstruction of the upper airway, the patient was admitted to hospital for monitoring of apnoeic episodes and treatment optimization, including use of continuous positive airway pressure until the patient underwent an adenotonsillectomy.

The laboratory tests revealed thrombocytopenia (90 000 platelets/mm$^3$; mean platelet volume, 12 fL), with normal white blood cell, haemoglobin, coagulation and platelet aggregation results, and the blood smear evinced anisothrombia and hypogranular platelets. The measurement of immunoglobulins evinced a minimal elevation of IgG, chiefly on account of IgG1, and persistent elevation of vitamin B12 (maximum, 2763 pg/mL). The quantitative lymphocyte panel revealed a CD3+TCRαßCD4−CD8−percentage of 1.6% (normal range, <2%), an inverted CD4/CD8 ratio, a CD325+/CD3DR+ ratio of 0.9 (normal range >1) and a memory B cell percentage of 10% (decreased). The workup was expanded with a bone marrow aspiration due to the presence of cytopaenia, adenopathy and organomegaly, and the bone marrow analysis did not find evidence of infiltration, haemophagocytosis, myelofibrosis or storage diseases.

Next-generation sequencing (NGS) was also performed with a panel that included genes involved in hereditary cytopaenias and immunodeficiencies, leading to the detection of a compound heterozygous variant in the gen *NBEAL2* gene (NM_010575.2:c.5497G>A, p.[E1833K] and NM_010575.2:c.3592C>T, p.[Q1198*]), compatible with GPS. Carrier status was later confirmed in the father.

During the course of disease, the patient experienced recurrence of tonsillar hypertrophy and new episodes of parotitis that required treatment with anti-inflammatory drugs and, in some instances, antibiotherapy. The patient has yet to develop bleeding diathesis. The splenomegaly remained stable, and the hepatomegaly resolved and was absent at the time of this writing. When it comes to hepatomegaly, its presence, detected at admission, did not seem to be directly related to GPS and was associated with mononucleosis syndrome.

Gray platelet syndrome is a rare inherited platelet disorder characterised by the marked deficiency or absence of α-granules, which contain compounds essential for coagulation, inflammation, wound healing and other processes. Clinically, patients exhibit moderate thrombocytopaenia and bleeding diathesis of varying severity. Examination of blood smears reveal enlarged agranular platelets with a grey appearance. In our patient, the records occasionally reported hypogranular platelets, but not clearly described as agranular or having a grey hue. The rarity of this disease hinders its diagnosis based on features observed in

the blood smear and requires a high level of suspicion, but these findings combined with a high platelet volume should be considered suggestive of GPS. Platelet aggregation tests with the usual inducers can also be useful for characterising the thrombocytopaenia, although in our patient the results were normal. Until a few years ago, the gold standard of diagnosis was the examination of platelets with electron microscopy, but this method is unavailable in many facilities. In this context, new genomic techniques such as massive gene sequencing acquire considerable relevance,[3] and have been added to the diagnostic algorithms for patients with suspected hereditary platelet disorders or thrombocytopaenias. Molecular diagnosis helps reach the definitive diagnosis, but is also useful for carrier screening and genetic counselling.

The workup would not include bone marrow aspiration or biopsy if peripheral thrombocytopaenia was suspected from the outset, unless other clinical or laboratory features suggested the presence of malignant disease, bone marrow failure or another diagnosis, as occurred in the case at hand.

The differential diagnosis included autoimmune lymphoproliferative syndrome (ALPS) and other lymphoproliferative disorders that could explain the presence of adenopathy, organomegaly and cytopaenia, even with normal CD3+TCRαßCD4−CD8− lymphocytes.[4,5] Furthermore, although elevation of vitamin B12 levels is a typical finding in these syndromes, it has also been observed in patients with GPS and other disorders, such as promyelocytic leukaemia, polycythaemia vera or hypereosinophilic syndrome, so clinicians should be mindful of this potential warning sign.

In recent years, there has been increasing evidence of the role of the relevance of the NBEAL2 protein in immunity, and of its absence potentially altering the function of granules in lymphoid and myeloid cells. Thus, *NBEAL2*−/− knockout mice exhibited increased susceptibility to viral and bacterial infections, secretory granule deficiency in neutrophils and NK cells and hypogranularity in monocytes. In addition, a recent review of patients with GPS demonstrates that up to 90% of patients exhibit immune system abnormalities, low white blood cell counts—not associated with myelofibrosis—or autoimmune disorders.[6] Therefore, this syndrome should be conceived as something more than a bleeding disorder, and groups should join efforts and collaborate to achieve a better understanding of the disease.

We ought to reinforce that GPS can be a cause of thrombocytopaenia and splenomegaly, and the particular importance of the blood smear examination and measurement of the mean platelet volume. Furthermore, given the potential impact of this syndrome beyond platelet aggregation, the suspicion of GPS should be expanded to include patients with splenomegaly and elevation of vitamin B12.

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