Hypergammaglobulinemia D and Periodic Fever Syndrome (HIDS) in a 3-year-old Patient from Puerto Rico

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Mevalonate kinase deficiency is a rare autosomal recessive disease caused by mutations in the mevalonate kinase gene (*MVK*). Depending on the mutations, a patient with this deficiency can exhibit any one of a spectrum of rare autoinflammatory diseases, such as hypergammaglobulinemia D (hyper-IgD) with periodic fever syndrome and mevalonic aciduria. To date, approximately 300 cases with mutations in the *MVK* gene have been reported worldwide. Herein, we present a 3-year-old female from Puerto Rico with a history of fever, arthralgia, and skin lesions since her first month of age and who, upon genetic workup, was confirmed to have compound heterozygous mutations in the *MVK* gene. Given her medical history and the results of her genetic testing, she was diagnosed with hyper-IgD with periodic fever syndrome. She will be treated with canakinumab, an interleukin-1ß antagonist, after receiving the varicella and measles–mumps–rubella (MMR) vaccines.

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Mevalonate kinase deficiency (MKD) is a rare autosomal recessive disease caused by a mutation in the mevalonate kinase gene (*MVK*) (1). This gene encodes for the enzyme MK, a key enzyme in the biosynthesis of cholesterol and isoprenoids. Depending on the mutations, the severity of the disease can vary across a spectrum of rare and autoinflammatory conditions, ranging from hypergammaglobulinemia D and periodic fever syndrome (HIDS) on the milder end, to the severe end of the MKD spectrum, mevalonic aciduria (MA) (1,2). According to data from the Eurofever registry, an international registry of autoinflammatory diseases, at least 300 people worldwide are affected by MKD (2), which disease presents mainly in individuals of European descent (3).

Patients with the HIDS phenotype are characterized by febrile attacks accompanied by lymphadenopathy, arthralgia, abdominal pain, diarrhea, vomiting, skin rash, aphthous ulcers, splenomegaly, and, rarely, progression to amyloidosis (3–6). These attacks tend to occur in the first year of life and can be provoked by several factors, including vaccinations, infections, minor trauma, surgery, and other physical or emotional stresses (3,4).

Here, we report on the first case of MKD in Puerto Rico, which was diagnosed in a 3-year-old female who had experienced recurrent fevers and skin rashes since the age of 5 weeks.

Case report

A 3-year-old female was brought by her parents to a rheumatology clinic in Puerto Rico with a history of unexplained fevers, lymphadenopathy, arthralgia, and skin rashes that started when she was a neonate. A review of her medical records revealed no history of having been vaccinated and multiple hospitalizations throughout her 3 years of life. Her symptoms began when she was 5 weeks old with the development of tumid, red infiltrated plaques on her left cheek (Figure 1A), prompting her hospitalization. These lesions had spread to other parts of the body: the upper and lower extremities, periumbilical area, buttocks, and eyes (Figure 1 B and C). The absence of fever and both anorexia and weight loss was also noted . During this period, the differential diagnosis was impetigo vs. herpes simplex virus (HSV), for which she received intravenous vancomycin, gentamycin, acyclovir, and erythromycin ophthalmic drops, with no improvement. Next, HSV was ruled out due to a negative test, and the acyclovir was discontinued. While hospitalized, she developed respiratory distress, leading to an oxygen desaturation of 84% to 86%. Afterward, she experienced near-monthly hospitalizations due to fever, skin rash, anorexia, arthralgia, cervical lymphadenopathy, leukocytosis, and elevated inflammatory markers that remained for around 4 to 5 days. Over time, she received multiple diagnoses, including Sweet syndrome and occult bacteremia. Of the several treatments attempted (e.g., steroids, NSAIDS, systemic and topical antibiotics, and antivirals), only prednisone succeeded in relieving the child's symptoms.

Current medical history noted a slight developmental delay in the patient's speech and motor skills, assessed using the third edition of the Ages and Stages Questionnaire. The physical exam was remarkable for left ankle inflammation and tenderness, abdominal

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pain, erythematous plaques on the left elbow, and cervical lymphadenopathy. A punch biopsy was taken from the lesions on her left elbow by the dermatology service (Figure 1D). The biopsy results indicated psoriasiform hyperplasia of the epidermis and edema of the papillary dermis. Additionally, there was a perivascular infiltration of lymphocytes and scattered neutrophils, along with the exocytosis of a few neutrophils into the epidermis (Figure 2).

The laboratory results revealed a high lactate dehydrogenase level: 308 U/L (reference range [RR]: 125–243). Her IgA, IgG, IgE, IgM, and IgD levels (130 mg/dL, 993 mg/dL, 80 IU/mL, 68 mg/dL, and 14 mg/dL, respectively) were within the normal ranges, and her liver enzymes, creatinine, electrolytes, and ferritin were also in the normal ranges. Her natural killer cell (NKC) count and absolute NKC levels showed elevated counts of 18% (RR: 2–16%) and 1134 cells/uL (RR: 95–620), respectively. The erythrocyte sedimentation rate (ESR) was also elevated, at 78 mm/hr (RR: 0–10). Table 1 summarizes the C-reactive protein, white blood count, and ESR levels from several of her hospitalizations over the years.

Given her past medical history, an autoinflammatory syndrome was suspected, and a genetic analysis was ordered. The autoinflammatory panel revealed compound heterozygosity at the MVK gene for the variants c. 1129G>A (p.Val337Ile) and c.664del (p.Ser22Hisfs*3), pointing to the diagnosis of MKD. Genetic testing of her parents revealed the mutations c.664del (p.Ser22Hisfs*3) and c.1129G>A (p.Val337Ile), from the father and mother, respectively. We advised the parents to allow the administration of the varicella and measles–mumps–rubella (MMR) vaccines before initiating canakinumab treatment in the patient in the subsequent months.

Discussion

Mevalonate kinase deficiency is a group of autoinflammatory diseases caused by defects in the *MVK* gene, resulting in a decrease or complete absence of the MK enzyme. The link between reduced MK activity and autoinflammation is thought to be a defective protein prenylation and not the accumulation of mevalonic acid (7). The reduction of these end products leads to the activation of inflammasomes and the secretion of the cytokines interleukin-1ß (IL-1ß) and IL-18 (8). These cytokines are responsible for the rise of the systemic inflammatory response typically seen in autoinflammatory pathologies (9).

To date, 282 mutations have been reported in the MVK gene, and around 180 are classified as pathogenic or likely pathogenic (10). The most common mutation found in the gene associated with MKD is p.Val377Ile. This mutation is commonly associated with the HIDS phenotype but has also been found in patients with more severe manifestations (7). The genetic testing in our patient showed compound heterozygosity with p.(V337I) and p.(Ser22Hisfs*3), the latter being a novel and potential pathogenic mutation not previously reported in the literature.

Figure 1. Skin lesions. A) Onset of first lesions at 5 weeks old, with a honey crust appearance. B) Development of lesions scattered over the face, observed 3 days after the initial eruption. C) Spreading of plaques throughout the body approximately 15 days following the appearance of the initial lesions. D) Tumid, red, discoid plaques with raised vesicular borders and central clearing on left elbow, where the biopsy was taken when she was 3 years old.

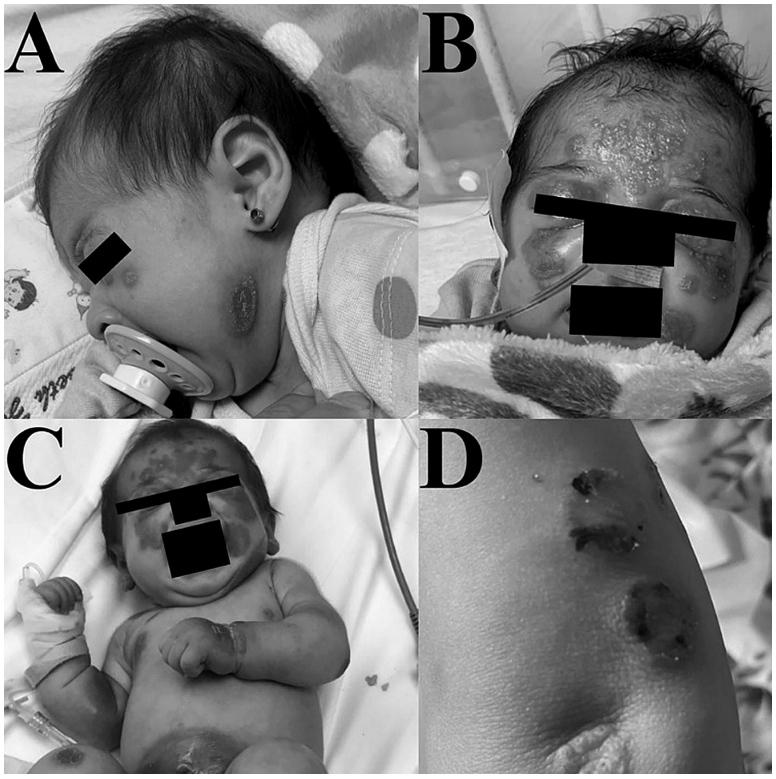

Figure 2. Hematoxylin and eosin stain of last punch biopsy taken from erythematous plaques on the left elbow. A) Histology of the biopsy in 4x showing irregular psoriasiform hyperplasia of the dermis. B) Same biopsy in 10x revealing absence of granular layer, neutrophil margination to the interstitial dermis, and some exocytosis into the epidermis.

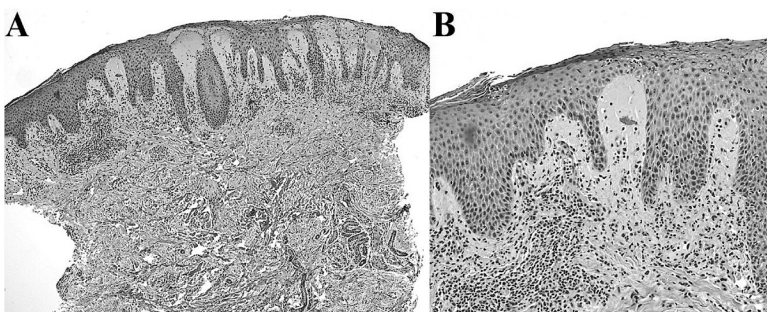

Table 1. Inflammatory markers during hospitalizations

	Dates						
Inflammatory marker	**9/13/20**	**6/28/21**	**10/21/21**	**04/14/22**	**07/13/22**	**01/19/23**	**05/20/23**
ESR (mm/hr) RR: 0–10	104	22.4	70	-	-	89	130
CRP (mg/dl) RR: 0.00–0.29)	22.06	14.90	43.80	-	-	12.40	21.30
WBC (x103/uL) RR: 4.6–10.2	24.5	22.4	19.6	24.3	19.4	20.6	12.8

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RR, reference range; WBC, white blood count.

The laboratory findings were not specific. However, inflammatory markers and leukocytosis have been reported in patients with HIDS (4). Immunoglobulins A and D (IgA and IgD, respectively) were found in the normal ranges, but this has also been seen before, and it is understood that there is no correlation between IgA and IgD levels and the presence of HIDS or its severity (11). The increased NKC count and absolute NKC levels seen in our patient correlate with inflammasome activation and the release of IL-18, both of which actions are critical checkpoints in the activation of NK cells (12).

The findings of the skin biopsy, combined with the patient's clinical presentation, past medical history, and genetic testing, led us to the diagnosis of MKD with the HIDS phenotype. This is supported by the appearance of the symptoms commonly associated with HIDS, including arthralgias, skin rashes, lymphadenopathies, and fevers, all of which persist for a few days before spontaneously resolving. Patients with the MA phenotype have been reported to have significant central nervous system involvement, presenting with psychomotor retardation, seizures, ataxia, myopathies, facial dysmorphisms, and, commonly, infant death (13). None of the previous were present in our patient. Because the patient has no history of having been vaccinated, we recommended administering the varicella and MMR vaccines before initiating canakinumab therapy.

Resumen

La deficiencia de Mevalonato Quinasa es una enfermedad rara autosómica recesiva causada por una mutación en el gen de Mevalonato Quinasa (*MVK*). Dependiendo en la mutación, los pacientes pueden presentar con un espectro de enfermedades auto inflamatorias raras como el Síndrome de Hipergammaglobulinemia D (hiper-IgD) con fiebre periódica y aciduria mevalónica. A estas fechas, aproximadamente más de 300 casos han sido reportados en el mundo con mutaciones en el gen de *MVK*. En este reporte, presentamos a una paciente de 3 años de Puerto Rico con un historial de fiebres, artralgia y lesiones en la piel desde su primer mes de nacida, la cual fue confirmada genéticamente de tener una mutación heterocigota compuesta en el gen de *MVK*. Dado su historial médico y los resultados de las pruebas genéticas, fue diagnosticada con el síndrome de hiper-IgD con fiebre periódica. La paciente será tratada con canakinumab, un antagonista de interleucina-1ß , luego de recibir las vacunas de varicela y sarampión-paperas-rubeola (MMR).

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