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Case Report

Humoral immunodeficiency in a patient with Malan syndrome secondary to chromosome 19p13.2 microdeletions

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Abstract

Malan syndrome (Sotos Syndrome 2, OMIM 614753) is a rare autosomal dominant overgrowth disorder caused by either chromosome 19p13.2/19p13.13 microdeletion or Nuclear Factor 1 X-Type (*NFIX*) gene haploinsufficiency. Symptoms typically appear in infancy and include dysmorphic features, seizures, and behavioral issues; however, the degree of immune system involvement is not clear. Herein, we are reporting a case of Malan syndrome who presented to the immunology clinic with recurrent bacterial infections, including three episodes of pneumonia confirmed by chest X-ray. Upon further work-up, the patient was found to have hypogammaglobulinemia (IgG 115mg/dL with reference range 445-1,187mg/dL) and poor response to Haemophilus influenzae type B vaccine (<0.11mg/L) and Prevnar vaccine (only 6 out of 12 serotypes were > 1.3 mcg/mL). The frequency of infections decreased dramatically after starting IgG replacement therapy. This case highlights the importance of conducting an immunology work-up in patients with recurrent Pneumonia, especially in patients with chromosomal disorders. Also, Malan syndrome can be associated with significant humoral immunodeficiency (hypogammaglobulinemia), requiring IgG replacement therapy.

Keywords: Malan syndrome, *NFIX gene* haploinsufficiency, Sotos Syndrome 2, Immunodeficiency, Hypogammaglobulinemia, IgG replacement therapy

Introduction

Malan syndrome (Sotos Syndrome 2, OMIM 614753) is an autosomal dominant overgrowth genetic disorder characterized by dysmorphic facial features, macrocephaly, intellectual disability, and behavioral issues [1]. This disease was first described in 2010 by Valerie Malan [2] and is extremely rare with approximately 80 reported cases worldwide (per the latest update from the orpha.net database). It is caused by either chromosome 19p13.2/19p13.13 microdeletion or Nuclear Factor 1 X-Type (*NFIX*) gene haploinsufficiency. Although the exact mechanism of this syndrome is not clear, the mouse model of NFIX shows an increased number of neurons and glia within the adult neocortex, likely due to the prolonged neurogenic window [3,4]. The effect of the *NFIX* gene haploinsufficiency on the immune system is not clear. Herein, we are reporting a case of Malan syndrome secondary to chromosome 19p13.2-19p13.3 microdeletion who presented to the immunology clinic with recurrent bacterial infections and was found to have significant humoral immunodeficiency (Common Variable Immunodeficiency-like disease) which required IgG replacement therapy.

Case Presentation

A4-year-old girl with Malan syndrome presented to the immunology clinic for evaluation of recurrent bacterial infections. She was born full-term and was admitted to the NICU due to feeding difficulty and recurrent desaturation. Initially, the desaturation resolved with positioning; however, due to the dysmorphic facial features and the intermittent episodes of stridor, laryngoscopy was performed and showed possible laryngomalacia. She was discharged on 0.5 L of oxygen via nasal cannula three weeks later. Soon after discharge, she was brought back to the hospital due to frequent apnea alarms and feeding difficulties. She was found to have hypercapnia and her sleep study suggested the diagnosis of obstructive apnea. Therefore, she was started on CPAP (Continuous Positive Airway

Pressure). Cranial 3D CT (computerized tomography) showed Pierre robin sequence and craniosynostosis. Mandibular reconstruction was performed at the age of 3 months by plastic surgery.

She was diagnosed with lissencephaly based on MRI (magnetic resonance imaging) shortly after birth and subsequently was found to have seizures and was started on antiepileptics. She also had G-tube with Nissen that was placed to manage the feeding issues. Of note, an echocardiogram showed normal anatomy and function. Microarray showed partial deletion of Chromosome 19 (2.2 megabase microdeletion 19p13.2-19p13.3), consistent with the diagnosis of Malan syndrome.

Over the following years, she had multiple ear infections (almost once per month). Given the frequency of the ear infections and the impact of these infections on the quality of life and seizure control, bilateral myringotomy with PE tube placement and adenoidectomy were done at one year of age. She had a tonsillectomy and second ear tube set at the age of three years for recurrent ear infections. She also had three episodes of Pneumonia, all proven on chest X-ray. Typically, she needed a prolonged antibiotic course to recover from the bacterial infections. She missed 3-5 days/month of school on average either due to increased seizure frequency in association with infection or due to hospitalization for IV antibiotics administration. She did not have any history of skin abscess or oral thrush. There was no significant family history of immune-related diseases except for her brother who has asthma and environmental allergy.

The immunology evaluation revealed low IgG 174 mg/dL (Reference range: 445-1,187 mg/dL), low IgA 21.6 mg/dL (Reference range: 25-153 mg/dL), low IgM 20.8 mg/dL (Reference range: 41-186 mg/dL) a poor response to Haemophilus influenzae type B vaccine (<0.11 mg/L; Reference range: >1.0 mg/L) and Prevnar vaccine (6 out of 12 serotypes were > 1.3 mcg/mL), and she had low switched memory B cells percentage (**Table 1**). Initially, the frequent ear infections were thought to be due to abnormal

Table 1: Baseline laboratory evaluation.

	Reference range	Results
Complete Blood Count		
White Blood Cells	5.0 - 14.5 thou/uL	7.75
Red Blood Cell Count	4.00 - 5.20 mil/uL	4.89
Hemoglobin	11.5 - 15.5 g/dL	13.0
Hematocrit	35 - 45%	40.2
MCH	25.0 - 33.0 pg	26.7
MCHC	31.0 - 37.0 g/dL	32.5
MCV	77.0 - 95.0 fL	82.1
Platelets	150 - 450 thou/uL	359
Mean Platelet Volume	7.4 - 10.4 fL	8.3
RBC Dist Width	12.5 - 16.0%	15.8
Monocytes	3 - 10%	5.5
Lymphocytes	24 - 54%	43.6
Neutrophils	34 - 56%	48.6
Eosinophils	0 - 5%	1.4
Basophils	0 - 2%	0.9
Immunoglobulin levels		
Immunoglobulin A (IGA)	25 - 153 mg/dL	21.6 (L)
Immunoglobulin E (IGE)	<142 KU/L	3.90
Immunoglobulin G (IGG)	445 - 1,187 mg/dL	174 (L)
Immunoglobulin M (IGM)	41 - 186 mg/dL	21.6 (L)
T, B, NK cell flowcytometry		
CD3% (pan T-cells)	54 - 79%	79
CD3 absolute count	1,051 - 3,031/mm^3	2,230
CD3+CD4+% (T-helper cell)	28 - 49%	59 (H)
CD3+CD4+ absolute count	548 - 1,720 / mm^3	1,658
CD3+CD8+% (T- cytotoxic cells)	17 - 32%	17
CD3+CD8+ absolute count	332 - 1,307 / mm^3	491
CD4/CD8 ratio	0.98 - 2.51	3.47 (H)

CD19% (pan B-cells)	9 - 32%	16
CD19 absolute count	203 - 1,139 / mm^3	440
CD3-CD16CD56+% (NK cells)	6 - 25%	5 (L)
CD3-CD16CD56+ absolute count.	138 - 1,027 /mm3	146
Isotype-switched memory B cell	1.14 - 26.87% of B Cells	0.90 (L)
Isotype-unswitched memory B cell	0.65 - 11.96% of B Cells	4.51
Naive B cells	54.85 - 96.02% of B Cells	93.78
Plasmablast	0.00 - 4.23% CD19 B Cells	0.02

facial anatomy. However, she continued to have frequent infections despite bilateral myringotomy, tonsillectomy, and adenoidectomy. Immunology workup showed significant hypogammaglobulinemia with poor vaccine response. The differential diagnosis of hypogammaglobulinemia includes either lack of IgG production or increased IgG loss in the stool or urine. IgG loss is associated with hypoalbuminemia which was absent in this case, therefore the lack of IgG production is likely the main cause of hypogammaglobulinemia. Furthermore, she had low switched memory B cells and poor vaccine response, suggesting a defect in the humoral immune system. Lastly, these findings can be seen in patients who receive immunosuppressive agents such as rituximab; however, this patient did not receive such therapy [5].

The patient was treated with prophylactic antibiotics (Trimethoprim and Sulfamethoxazole, once daily); however, she continued to have recurrent ear infections. Five months later, she was started on monthly intravenous IgG replacement (IVIG) therapy due to significant hypogammaglobulinemia and the persistence of recurrent infections despite the antibiotic prophylaxis. Although the IVIG corrected her hypogammaglobulinemia and reduced the frequency of infections, she had more seizures around the time of the IVIG infusions. Ultimately, she was switched to subcutaneous IgG therapy (**Figure 1**). The patient tolerated the subcutaneous IgG infusion without major side effects for the last 4 years. The frequency of infections decreased significantly after starting the IgG replacement therapy to 3-4 ear infections per year. Moreover, she did not have any pneumonia for the last 6 years.

Discussion

This case highlights the immunological features of Malan syndrome secondary to chromosome 19 microdeletion (19p13.2-19p13.3) which includes low immunoglobulins (IgA, IgM, and IgG), decreased switched memory B cells, and poor vaccine response to Haemophilus influenzae type B and Prevnar vaccines.

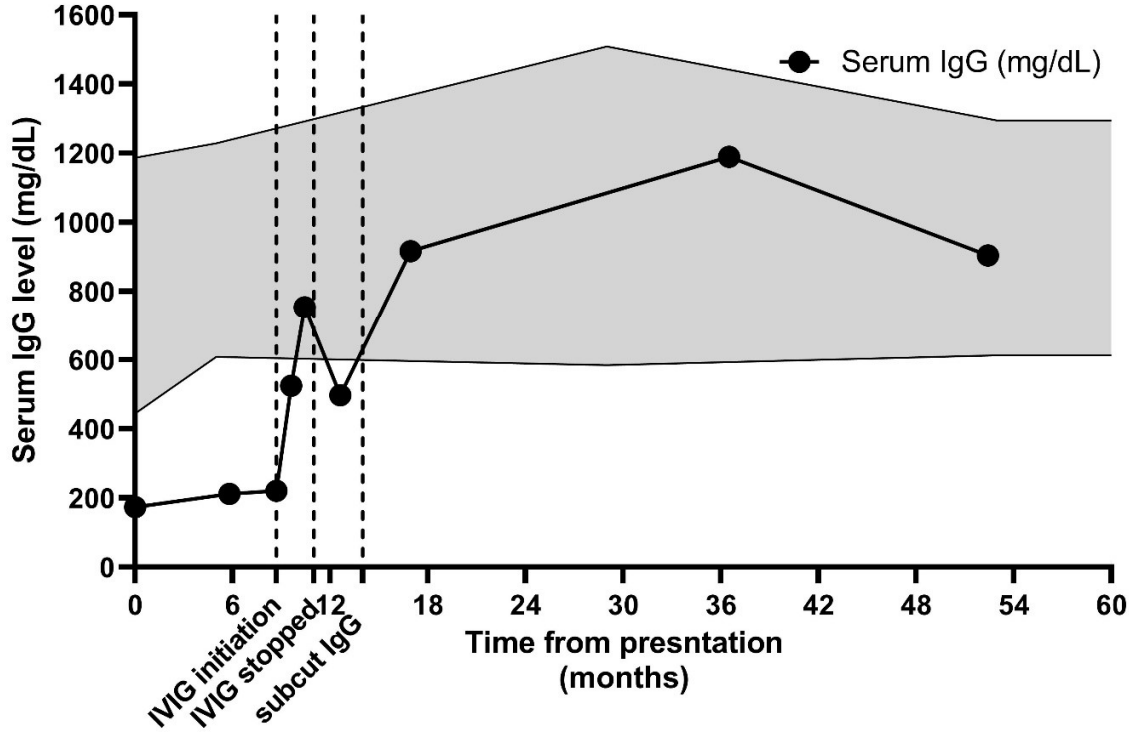

Figure 1: Serum IgG levels over time.

These are the same features seen in patients with common variable immunodeficiency: however, that diagnosis is typically reserved for patients without chromosomal abnormalities [6]. Also, this patient improved with IgG replacement therapy as expected in patients with humoral immunodeficiency.

Despite the early diagnosis of this patient with Malan syndrome and the significant history of recurrent infections, the work-up for immunodeficiency was delayed until the age of 5 years due to the lack of known association between immunodeficiency and this syndrome. Initially, the medical team attributed the frequent infections to abnormal facial features and narrow airways which were well reported in the literature [7]. However, when the patient did not improve, an immunology referral was provided. In the most comprehensive study to date, Priolo et al. detailed the features of Malan syndrome from 45 patients through international collaboration and compared them to 35 previously reported patients. The typical facial features include macrocephaly (which may decrease with age) with prominent forehead, triangular face (which becomes more elongated with age), prominent chin, small mouth with an everted lower lip, long philtrum, short nose with anteverted nares, and depressed nasal bridge [7]. Visual problems and intellectual disability are very common with variable degrees of disease severity and seizures occur in 18-27% of the patients [7]. Only one patient from that report had increased susceptibility to infection. However, it is unknown if the other patients had recurrent infections.

There was no clear genotype-phenotype correlation in Malan syndrome except for the higher risk of seizures with 19p13.2 microdeletions in comparison to *NFIX* haploinsufficiency [7]. This could be due to the deletion of the CACNA1A gene (OMIM 601011), which is linked with epilepsy and encodes neuronal voltage-gated calcium channel [8,9]. Our patient had microdeletion 19p13.2-19p13.3 which includes many genes besides the *NFIX* gene. Therefore, we cannot be certain if the immunodeficiency is due to *NFIX* deletion or any other gene in the same area. The patient with increased susceptibility to infection from Priolo et. al. had *NFIX* gene haploinsufficiency, which suggests that *NFIX* deletion is the likely culprit in our case. Of note, the *NFIX* gene is widely expressed in human tissues, including the bone marrow and lymphoid tissues (proteinatlas.org/ENSG00000008441-NFIX/tissue). Therefore, it is conceivable to have immunodeficiency secondary to the *NFIX* gene deletion. More mechanistic studies are needed to delineate the role of the *NFIX* gene in various immune cells.

Conclusions

- Immunology work-up should be considered in patients with chromosomal disorders and a history of recurrent infections.
- Malan syndrome can be associated with significant humoral immunodeficiency requiring IgG replacement therapy.
- IgG replacement therapy can lead to a significant reduction of infection burden in patients with hypogammaglobulinemia and poor vaccine response.

Data Availability

The data that support the findings of this case report is available from the corresponding author (Amer Khojah) upon reasonable request.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article

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