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LETTER TO EDITOR

Immunodeficiency in a Child with 22q11.2 Microduplication Syndrome

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Dear Editor,

We present the case of a 6-year-old girl with 22q11.2 microduplication syndrome (22q11.2q11.2 D22s75++) and detail the immunological features of such a case.

Case Report

Our patient's diagnosis was made in infancy after screening for 22q11.2 deletion syndrome in the context of her congenital heart disease (hypoplastic left heart syndrome). Other clinical features noted at the time included facial dysmorphism (upslanted palpebral fissures, flat nasal bridge) and developmental delay. In early childhood, she was particularly susceptible to respiratory tract infections and was noted to be lymphopenic ($0.9–2.0 \times 10^9$/L). She also had transient hypogammaglobulinemia of infancy. Lymphocyte immunophenotyping subsequently demonstrated T cell lymphopenia with counts of 765 cells/μL, helper T cell counts of 540 cells/μL (55 % naive), and cytotoxic T cell counts of 213 cells/μL (58 % naive) at the age of 4. Her B cell count was normal (385 cells/μL) with 6 % class-switched memory B cells and normal NK cell numbers (183 cells/μL). Serum IgG (7.4 g/L), IgA (0.51 g/L), and IgM (1.83 g/L) levels were in the normal range for her age at the time. Vaccine-specific antibody responses to *Haemophilus influenzae B*, tetanus, and pneumococcus were robust. Our patient demonstrated a normal T cell proliferation response to phytohemagglutinin and a normal TCR-vβ repertoire. Despite having a good population of naive T cells, a T cell receptor excision circle (TREC) assay demonstrated a relatively low copy number (1269 copies/10^6 T cells). Our patient was prescribed prophylactic antibiotic therapy (azithromycin) and subsequently had fewer respiratory tract infections. She later developed intermittent mild neutropenia ($0.6–1.4 \times 10^9$/L) and was found to be anti-neutrophil antibody positive, but has neither had significant infections nor required support with gCSF.

Discussion

In 1999, Edelmann et al. demonstrated by FISH the first case of a patient with an interstitial duplication of the 3-MB region commonly deleted in velocardiofacial/diGeorge syndrome [1]. The first patient described had subtle facial dysmorphism, developmental delay, and epilepsy. A review of 22q11.2 microduplication syndrome published 10 years later documented 50 cases in total with a broad and varied phenotype including many features commonly seen in 22q11.2 deletion syndrome (heart defects, urogenital abnormalities, and velopharyngeal insufficiency) but did not mention immunodeficiency [2]. Portnoi et al. estimated the incidence of 22q11.2 microduplication to be approximately half that of 22q11.2 microdeletion, with a higher proportion of familial duplications, decreased penetrance, and greater intrafamilial phenotypic variation [2]. One case with thymic aplasia, asplenia, and associated severe immunodeficiency was described by Ensenauer et al. in a case series published in 2003 [3]. Three siblings with 22q11.2 microduplication and increased susceptibility to infection are mentioned in a case

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series by Engels et al. but their immunophenotype is not described [4].

The incidence of increased susceptibility to infection, while not well described in the medical literature, is evident from the experience of patients with 22q11.2 microduplication as documented in a publication from UNIQUE, the rare chromosomal disorder patient support group (http://www.rarechromo.org/information/Chromosome%2022/22q11.2%20duplications%20FTNW.pdf). The phenotype described is similar to that seen in our patient, with increased susceptibility to respiratory tract infections being the most prominent. The likelihood is that they may well also have features reminiscent of a "partial" diGeorge as we have described in our patient, with a relative reduction in T cell numbers, and increased susceptibility to autoimmunity.

To conclude, we suggest that patients with 22q11.2 microduplication syndrome may have an immunological phenotype similar to those with 22q11.2 microdeletion syndrome, have the potential to be susceptible to both infection and autoimmunity, and should be evaluated and monitored in a similar manner.

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