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The immune deficiency of chromosome 22q11.2 deletion syndrome

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The syndrome originally described by Dr. Angelo DiGeorge had immunodeficiency as a central component. When a 22q11.2 deletion was identified as the cause in the majority of patients with DiGeorge syndrome, the clinical features of 22q11.2 deletion syndrome became so expansive that the immunodeficiency became less prominent in our thinking about the syndrome. This review will focus on the immune system and the changes in our understanding over the past 50 years. Initially characterized as a pure defect in T cell development, we now appreciate that many of the clinical features related to the immunodeficiency are well downstream of the limitation imposed by a small thymus. Dysfunctional B cells presumed to be secondary to compromised T cell help, issues related to T cell exhaustion, and high rates of atopy and autoimmunity are aspects of management that require consideration for optimal clinical care and for designing a cogent monitoring approach. New data on atopy are presented to further demonstrate the association.

KEYWORDS
allergy, DiGeorge, IgG, malignancy, T cells

1 | INTRODUCTION

DiGeorge syndrome, autosomal dominant Opitz GBBB, Sedlackova syndrome, Caylor cardiofacial syndrome, Shprintzen syndrome, and conotruncal anomaly face syndrome have all been demonstrated to be associated with 22q11.2 deletions (Burn et al., 1993; Caylor, 1969; Giannotti, Digilio, Marino, Mingarelli, & Dallapiccola, 1994; Matsuoka et al., 1998; McDonald-McGinn, Emanuel, & Zackai, 1996; Sedlackova, 1955; Shprintzen et al., 1978). All of these are variably associated with immunodeficiency and an important point is that severe immunodeficiency, requiring a thymus transplant or matched donor T cells, can occur in infants with or without cardiac anomalies (Markert et al., 2007). There is to date no phenotypic feature that predicts immune dysfunction other than thymic size (Sullivan et al., 1998). Thymic size is nearly impossible to measure because small rests of thymus can be hidden in the neck or mediastinal structures. A very small thymus seen on imaging or at the time of surgery does not necessarily predict low T cell counts. Thus, the immune system requires specific laboratory analysis.

Largely invisible to physical examination, the immune system which was first highlighted in the initial descriptions of DiGeorge syndrome (DiGeorge, 1968), later became somewhat marginalized as the physical features and clinical complications dominated the literature (McDonald-McGinn et al., 1999; Ryan et al., 1997). Dr. DiGeorge recognized the common embryologic source of the thymus, the heart and the parathyroid glands, thus leading to the terminology of DiGeorge syndrome when cardiac anomalies, thymic hypoplasia, and hypocalcemia co-occurred in an infant. The term "DiGeorge syndrome" is sometimes still utilized by immunologists who utilize the term "complete DiGeorge syndrome" to reflect an absence of T cells. This historical nomenclature is best reserved when the genetic cause of the phenotype is unknown. When 22q11.2 deletion status is known,

it is best to refer to that underlying etiology rather than confuse patients and other physicians with non-specific syndromic names.

The number of infants with a severe immunodeficiency requiring transplantation, is small compared to the overall number of affected infants. Nevertheless, immunodeficiency is common and surprisingly, can have a distinct phenotype in adulthood, a time period when not many patients are under the care of an immunologist (Gennery et al., 2002; Zemble et al., 2010). Recent data have demonstrated that the presence of an immunodeficiency is associated with increased medical costs across the entire spectrum of care types, suggesting that the more immune deficient patients have important needs (Sullivan, Burrows, & McDonald McGinn, 2016). This review will describe the clinical and laboratory features as well as some options for management.

2 | NEONATAL MANAGEMENT

Low T cell numbers are seen in 75–80% of infants with chromosome 22q11.2 deletion syndrome (22q11.2del) (Gennery, 2012). In most cases, the T cell count is moderately decreased and does not impact planned surgical procedures or care of the infant while hospitalized. Surgical infections are increased in this population (Mercer-Rosa, Pinto, Yang, Tanel, & Goldmuntz, 2013) and additional care may be prudent, however, there is no specific intervention for slightly low T cells. Fewer than 0.1% of patients with the deletion have absent T cells and these patients represent a special category that requires individualized care and are treated in the same manner as patients with severe combined immune deficiency (Ryan et al., 1997). Management of patients with absent T cells is discussed below.

Cardiac surgery may be required before analysis of the immune system can be performed. Ideally, a T cell count should be obtained prior to surgery if non-irradiated blood will be given. Flow cytometric analysis of T cells requires minimal blood and the results are typically available within 24 hr if performed on site. This allows a precise analysis of the T cell compartment. Many large centers irradiate all blood products given to infants to prevent graft versus host disease which can occur when infants with absent T cells are given allogenic cells. If necessary, the absolute lymphocyte count can act as an approximate surrogate for a T cell count. A lymphocyte count in a newborn should be greater than 2,800 cells/mm^3 (Gossage & Buckley, 1990). If the lymphocyte count is lower, precautions should be considered; however, it must be recognized that this is not a substitution for an analysis of T cells. In addition to concerns about graft versus host disease, infants with congenital heart disease are often given prophylaxis for respiratory syncytial virus. No studies have examined additional risks imposed by the presence of a 22q deletion.

A new category of identified infants are those who are brought to medical attention because of a positive newborn screen for severe combined immune deficiency (Verbsky et al., 2012). Nearly 80% of infants in the USA are now screened for T cell lymphopenia. This newborn screen detects all forms of T cell lymphopenia and more infants with 22q11.2del are identified than those with severe combined immune deficiency (Kwan et al., 2014). These children, as part of the newborn screening protocol will typically have an analysis of their immune system. This analysis in early infancy is designed to identify infants who will require transplantation. Infants with no or very low (<200 CD3 T cells/mm3) cannot defend against viruses properly and are at high risk of death from infection, as is true of patients with severe combined immune deficiency (Markert et al., 1998).

3 | MANAGEMENT OF PATIENTS WITH THYMIC APLASIA

The patients with true thymic aplasia and absent T cells require very specific care to prevent infections and graft versus host disease. Thymic transplantation is available at one center in the United States and one in the United Kingdom. Fully matched donor T cells have also been given as a therapeutic approach (Gennery et al., 2010; Land et al., 2007). 22q11.2del is responsible for thymic aplasia in slightly less than half of the patients with a DiGeorge type of picture and thymic aplasia. Therefore, lack of a deletion should not delay referral if there are consistent syndromic features and no T cells (Chinn, Devlin, Li, & Markert, 2008). The remainder of the cases are due to CHARGE syndrome or fetal toxin exposures . In principle, there should be no T cells with true thymic aplasia,. There are, however, a small number of infants who have high T cell counts of an oligoclonal expansion of T cells (Markert et al., 2004). These infants usually have a rash, hepatosplenomegaly, and eosinophilia and the T cells will have the memory phenotype. These infants paradoxically require immune suppression.

A thymus transplant or a fully matched T cell transplant is required for patients with thymic aplasia. An evaluation of the naïve T cell count in early infancy can be used to estimate the potential for thymic production of T cells, but the counts can change substantially over a few months. CD4/CD45RA T cells <50 cells/mm^3 on two separate occasions suggests a need for a transplant. Thymus transplant or a fully matched transplant of T cells (such that thymic education is not required) can be used. Thymus transplantation has been used more frequently and has superior outcomes (Goldsobel, Haas, & Stiehm, 1987; Janda et al., 2007; Markert et al., 2007). Thymic tissue is harvested from donors and cultured to remove mature T cells capable of causing graft-versus-host disease (Davis et al., 1997). Thin slices of thymus are implanted in the quadriceps muscle. Functional T cells appear at 90–100 days post transplantation (Davis et al., 1997). Subsequently, the implanted thymus involutes and does not produce T cells for a prolonged time. Patients develop a substantial T cell repertoire and have adequate host defense and are able to play and go to school in spite of moderate residual immune deficiency.

4 | MANAGEMENT OF MILD TO MODERATE T CELL LYMPHOPENIA

Early in life, those children with T cell counts in the range of CD3 = 800–2,000 cells/mm^3 have largely normal immunoglobulin levels and T cell proliferative responses (Bjork, Oskarsdottir,

Andersson, & Friman, 2012; Chinen, Rosenblatt, Smith, Shearer, & Noroski, 2003; Jawad, McDonald-Mcginn, Zackai, & Sullivan, 2001). Many adults with 22q11.2del have normal T cell numbers and this masks the important functional compromise in the older children and adults that arises over time as the T cells develop an exhausted phenotype (Jawad et al., 2011; Kanaya et al., 2006; Piliero, Sanford, McDonald-McGinn, Zackai, & Sullivan, 2004; Zemble et al., 2010).

Children with mild to moderate decrements in their T cell counts will often have an increase in the number of infections. Parents will describe that viral infections persist followed by the development of bacterial superinfection. An increased frequency of allergies may also contribute to the predisposition to bacterial superinfection (Staple, Andrews, McDonald-McGinn, Zackai, & Sullivan, 2005). The immune system represents a significant variable in the occurrence of infections but anatomy is also a major contributor. Relatively horizontal Eustachian tubes, compromised sinus drainage due to anatomical issues, tracheomalacia, and gastroesophageal reflux may all contribute to recurrent infections. Increased contact with the healthcare system may also be a risk for recurrent infections. Efforts to diminish infectious exposures through the use of hand hygiene can be useful and efforts to decrease colonization with xylitol-containing gum or antibiotic prophylaxis can be beneficial but cannot overcome some anatomical contributions. Treating or mitigating any allergies can also improve the infection pattern. Asthma occurs with higher frequency in patients with this syndrome and efforts to prevent wheezing and to aggressively treat wheezing during a viral infection can improve outcomes.

The risk of using live viral vaccines in infants appears to be low with the exception of patients with thymic aplasia and/or very low T cell counts. Both the MMR and the varicella vaccine were found to be safe and efficacious in children with the deletion who had mild to moderate T cell compromise (Hofstetter et al., 2014; Moylett, Wasan, Noroski, & Shearer, 2004; Perez, Bokszczanin, McDonald-McGinn, Zackai, & Sullivan, 2003). It would not be appropriate to give live viral vaccines to patients with severe T cell compromise in the range of CD4CD45RA counts <100 cells/mm3.

Laboratory studies in children with mild-moderate T cell compromise will usually reveal accelerated conversion of naïve T cells (CD4/CD45RA) to memory T cells (CD4/CD45RO). Low IgM and IgA levels are common and are not treatable, however, low IgG levels can be treated with immunoglobulin replacement and approximately 6% of children and adults with 22q11.2del syndrome will require treatment (Patel et al., 2012). IgA deficiency, impaired responses to vaccines and low IgG levels have all been described (Finocchi et al., 2006; Gennery et al., 2002; Smith et al., 1998) but occur in a minority of patients. A more severe infection pattern correlated with immunoglobulin abnormalities (Finocchi et al., 2006; Gennery et al., 2002). The immunoglobulin defects occur in spite of normal bone marrow production of B cells (Dar et al., 2015). Monitoring of T cell counts and immunoglobulin levels and titers every 2–5 years depending on the severity of the immune deficiency may be useful although best practices have yet to be defined in this population. The immune deficiency evolves over time and the low T cell counts with normal proliferation that characterize most children give way to increasing antibody deficits, poorer proliferation, and high levels of exhausted T cells as the children transition to adulthood. Not all adults have a significant immune deficiency and at this point it is not known if very low T cells in infancy predict worse immune deficiency in adulthood. Periodic monitoring is sensible given our lack of biomarkers for the evolving immune deficiency.

Adults with 22q11.2del syndrome have defects in T cell repertoire (deletions, oligoclonality) (Cancrini et al., 2005; Piliero et al., 2004) and short telomeres (Piliero et al., 2004). A compromised repertoire impairs responses to pathogens and short telomeres compromises proliferation. Apoptosis of lymphocytes is increased in adults which may be due to the short telomeres (Gupta, Aggarwal, & Nguyen, 1998). Compared to a population with HIV with similar T cell counts, patients with the deletion have much better immunologic function. Opportunistic infections are very infrequent (Ryan et al., 1997) and the most common type of infection is a respiratory viral infection.

5 | AUTOIMMUNE DISEASE

Autoimmune disease is significantly increased, with juvenile idiopathic arthritis and autoimmune cytopenias the most common (Davies, Telfer, Cavenagh, Foot, & Neat, 2003; Davies, Stiehm, Woo, & Murray, 2001; Jawad et al., 2001; Kratz et al., 2003). Idiopathic thrombocytopenia pupura is the most common of the autoimmune diseases although platelet size and number are slightly aberrant at baseline in most patients with the deletion (Lawrence, McDonald-McGinn, Zackai, & Sullivan, 2003). This is due to haplosufficiency for GP1Bβ. Celiac disease may be increased over the frequency in the general population (Digilio et al., 2003). The mechanism underlying the susceptibility to autoimmune disease is probably multifactorial with homeostatic expansion selecting for self-reactive T cells. Decreased regulatory T cells may also contribute to the predisposition to autoimmunity (Sullivan, McDonald-McGinn, & Zackai, 2002).

6 | ATOPY

Atopy and inflammation associated with a Th2 response have been described for many years in murine lymphopenia models and infants with Omenn syndrome, due to oligoclonal expansion of a few T cell clones in a lymphopenic environment (Khiong et al., 2007; Milner, Ward, Keane-Myers, & Paul, 2007; Wada et al., 2000). Direct identification of allergies in patients with 22q11.2del was limited to small series (Staple et al., 2005; Zemble et al., 2010) but was predicted based on the known effects of homeostatic proliferation. Because of the paucity of information, we performed a retrospective analysis of medical records at our institution. Children with a confirmed genetic diagnosis of 22q11.2del born August 2006–December 2013 were included. A total of 186 patients with sufficient information for analysis were examined by electronic record extraction. Allergy histories were cross referenced by direct examination of the record. Of those patients 143 had T cell subset information available. The

mean age of the cohort was 7.7 years. Seven patients had autoimmune disease (3.7%). We found evidence of atopic disease in two thirds of the patients. 41% had asthma, 32% had rhinitis, 15% had eczema, 11% had food allergy, and 19% had a drug allergy. In contrast, in the United States, upwards of 40% of children have allergic rhinitis, 8.5% have asthma, 10–20% have atopic dermatitis, and 4–6% have food allergies (Akinbami et al., 2012; Hanifin, Reed, Eczema, &ampImpact Working G, 2007; Liu et al., 2010; Nathan et al., 2008). We hypothesized that a greater degree of lymphopenia in infancy, driving greater homeostatic proliferation, would be associated with increased risk of atopy. To test this, we stratified according to the earliest CD3 T cell count available using commonly available normal ranges in an age adjusted manner (Comans-Bitter, de Groot, & van Dongen, 1996). With age, progressively fewer patients met the criteria of low CD3 T cells (Figure 1), as we had previously reported (Piliero et al., 2004; Sullivan et al., 1999). Having a low CD3 count was associated with increased atopy of 2.56-fold compared to those with a normal CD3 count ($p = 0.0071$). This association was not observed for CD4 or CD8 counts. Specific types of atopy are displayed in Figure 2. This finding is consistent with what has been observed in murine models of homeostatic expansion (Milner, Fazilleau, McHeyzer-Williams, & Paul, 2010; Milner et al., 2007). This study of patients from a single institution supports a prior study (Staple et al., 2005) and emphasizes atopy as a downstream consequence of limited T cell production in 22q11.2del.

7 | MALIGNANCY

Many immune deficiencies are associated with a predisposition to malignancy and severe cardiac anomalies can be associated with significant secondary immune deficiency (Morsheimer et al., 2016).

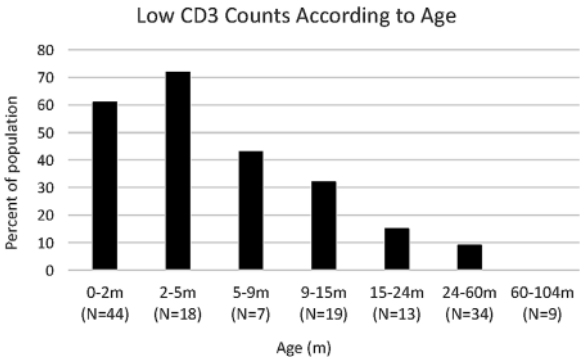

FIGURE 1 The frequency of low CD3 T cells stratified by age. The normative data developed for age (Comans-Bitter et al., 1996) was utilized to designate low T cell counts in patients of different ages. Less than 5% was used as the threshold to define low T cells. The age for each patient at the time of immunophenophenotyping was extracted and compared to the normative data. The graph indicates the frequency of patients with low T cells in each age bracket. With increasing age, the frequency of low T cells diminishes

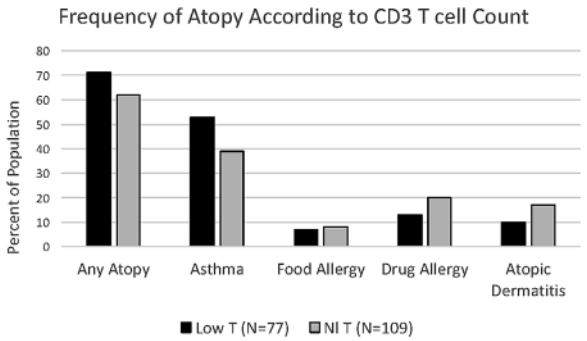

FIGURE 2 Atopic conditions stratified according to CD3 T cell count. We examined the types of atopic disease across the cohort stratified by low T cells, as described in Figure 1

Thus, the question of susceptibility to malignancy in 22q11.2del is pertinent. There are multiple case reports of individuals with malignancy. Wilms tumor has been reported twice while monoclonal lymphoid hyperplasia/lymphoma has been reported six times (Finch, Pivnick, Furman, & Odom, 2011; Hong et al., 2001; Itoh, Ohno, Kakizaki, & Ichinohasama, 2011; Pongpruttipan, Cook, Reyes-Mugica, Spahr, & Swerdlow, 2012; Ramos, Lopez-Laso, Ruiz-Contreras, Giancaspro, & Madero, 1999; Sato et al., 1999; Veerapandiyan, Chinn, Schoch, Maloney, & Shashi, 2011). A concerning report is the finding of myelodysplasia in 22q11.2del (Ozbek, Derbent, Olcay, Yilmaz, & Tokel, 2004). Additional case reports of xanthoastrocytoma, hepatoblastoma, and renal cell carcinoma support a possible susceptibility to malignancy (Murray et al., 2011; Scattone et al., 2003). Distal to the typical deletion are additional low copy number repeats and rare patients have a deletion that encompasses both the typical region and distal genes including the gene, *SMARCB1*, a tumor suppressor gene. There have now been eight individuals with this large deletion who present with features of 22q11.2del and rhabdoid tumors (Beddow, Smith, Kidd, Corbett, & Hunter, 2011; Bosse et al., 2014; Toth et al., 2011). These tumors are nearly unique to infancy and early childhood and most often affect the kidneys or CNS, however, they can affect any soft tissue. Deletion of *SMARCB1* can also be associated with familial schwannomatosis which has not yet been described in 22q11.2del. One study has systematically examined large cohorts for the occurrence of malignancy (McDonald-McGinn et al., 2006). In that study 687 people with 22q11.2del were examined. There were two patients with hepatoblastoma, one each with neuroblastoma, acute lymphoblastic leukemia, Wilms tumor, and thyroid carcinoma. The overall frequency of malignancy in the cohort was therefore less than 1%.

8 | SUMMARY

In infants, the crucial immunologic management decision is the identification of those who require transplantation for survival. Most families benefit from advice and guidance on the prevention and management of recurrent infection which compromise quality of life

and may drive up health care costs. As the children mature, periodic monitoring to detect evolving antibody defects is appropriate and intervention offered to treat a low IgG initiated when appropriate. Management of allergies can improve the infection pattern but anatomy is an important co-factor. Anticipatory guidance is valuable for the family and a comprehensive approach to the consequences of the immune deficit can markedly improve the quality of life.

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