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IMMUNE DEFICIENCY AND DYSREGULATION (DP HUSTON AND C KUO, SECTION EDITORS)

Immune and Genetic Features of the Chromosome 22q11.2 Deletion (DiGeorge Syndrome)

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Abstract

Purpose of Review This review provides an update on the progress in identifying the range of immunological dysfunction seen in DiGeorge syndrome and on more recent diagnostic and treatment approaches.

Recent Findings Clinically, the associated thymic hypoplasia/aplasia is well known and can have profound effects on T cell function. Further, the humoral arm of the immune system can be affected, with hypogammaglobulinemia and poor vaccine-specific antibody response. Additionally, genetic testing utilizing chromosomal microarray demonstrates a small but significant number of 22q11 deletions that are not detectable by standard FISH testing. The recent addition of a TREC assay to newborn screening can identify a subset of infants whose severe immune defects may result from 22q11 deletion. This initial presentation now also places the immunologist in the role of "first responder" with regard to diagnosis and management of these patients.

Summary DiGeorge syndrome reflects a clinical phenotype now recognized by its underlying genetic diagnosis, chromosome 22q11.2 deletion syndrome, which is associated with multisystem involvement and variable immune defects among patients. Updated genetic and molecular techniques now allow for earlier identification of immune defects and confirmatory diagnoses, in this disorder with life-long clinical issues.

Keywords DiGeorge syndrome · Chromosome 22q11 deletion · Thymic dysfunction · TREC assay

Introduction

Angelo DiGeorge, a pediatric endocrinologist practicing in Philadelphia, began studying a group of patients with both thymic aplasia and congenital hypoparathyroidism. In an extensive historical review of this disorder by Frank Greenberg, DiGeorge noted that thymic aplasia was first mentioned by Harrington in 1829, and an association between thymic aplasia and congenital hypoparathyroidism was described by Lobdell in 1959 [1]. At the time, DiGeorge stated, "the concurrent absence of both structures is not surprising if one recognizes that both are derived from common primordia. Furthermore, this association has been previously recorded although its physiologic significance has not been recognized." [1].

In 1968, DiGeorge and others described a series of patients with congenital absence of the parathyroid glands, and no visible thymic tissue [2]. Harold Lischner, an immunologist collaborating with DiGeorge, categorized developmental defects in the third and fourth pharyngeal pouches that led to the anatomic defects described by DiGeorge [3]. Complete DiGeorge syndrome was defined in cases of III-IV pharyngeal pouch syndrome in which no thymic tissue was noted on postmortem examination. Partial DiGeorge syndrome described cases of III-IV pharyngeal pouch syndrome with defective cell-mediated immunity or thymic hypoplasia measured by reduced thymic weight. These clinical classifications are now largely used to describe an immune phenotype,

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without distinction for the underlying etiology of the malformations, which could include chromosome 22q deletion, CHARGE syndrome, or an infant of a diabetic mother. By 1979, Conley further defined the core triad features of DiGeorge syndrome to include (i) complete or partial absence of the thymus and/or cellular immune deficiency, (ii) symptomatic hypocalcemia and/or parathyroid hypoplasia, and (iii) conotruncal cardiac outflow tract defects such as interrupted aortic arch type B and persistent truncus arteriosus [1]. Continued studies of these cases and others led to the realization that many showed chromosomal rearrangements that involved a small pericentromeric region of chromosome 22q11.2 and with the introduction of specific molecular cytogenetic tools in the early 1990s, an understanding of the genetic etiology underlying many of DiGeorge's cases evolved and became defined as the 22q11 deletion syndrome.

Genetic Findings

Deletion syndromes are caused by the loss of genetic material from a given chromosome with a resulting, often recognizable, phenotype. Many deletions have been detectable under the microscope during karyotyping (e.g., 1p-, 4p-, 5p-). The introduction of fluorescent probes for specific chromosomal regions for fluorescence in situ hybridization or FISH studies aided the detection of recurrent deletions not clearly visible on karyotype analysis. The limitations of FISH include that it is a targeted test, requiring enough clinical suspicion to identify the correct region for analysis. In addition, the test may miss deletions and duplications whose endpoints are outside the narrow region covered by the probe used for FISH. More recently, the use of chromosomal microarrays with dense, genome-wide coverage, has allowed the identification of smaller chromosomal deletions and duplications that are submicroscopic and undetectable by standard karyotyping and FISH techniques. The use of high-resolution microarrays in infants with multiple congenital anomalies has, in many cases, led to the identification of a specific genotype, with subsequent clinical investigations then further defining the associated phenotype [4]. The deletions of chromosome 22q11.2 are largely submicroscopic, have a recognizable but often variable phenotype, and show recurrent breakpoints in unrelated individuals [5••]. Many of these deletions are not detectable by standard FISH probes, with the proximal end of their breakpoints initiating after the locus used for FISH [6]. In aggregate, 22q11.2 deletions have proven to be the cause of the most frequently occurring microdeletion syndrome in humans, seen in 1:4000–1:5000 births.

The frequency of these deletions is related to the underlying architecture of the 22q11 genomic region and the presence of segmental duplications, or large, low copy blocks of DNA that contain chromosome-specific repetitive sequences [7]. The highly homologous segmental duplications can mediate misalignment and non-allelic homologous recombination (NAHR) resulting in deletion or duplication of the sequence located between the repeats [8]. Similarly, microdeletions of other chromosomes have been mechanistically tied to aberrant recombination due to the presence of local segmental duplications and have been found in regions of the genome prone to rearrangements. These include the pericentromeric regions of chromosomes 7q11, 15q11, and 17q11, resulting in the phenotypes seen in Williams-Beuren syndrome, Prader-Willi or Angelman syndrome, Charcot-Marie-Tooth disease, or hereditary neuropathy with liability to pressure palsies (HNPP), respectively [8].

The vast majority of patients (75–80%) have the same large 22q11 deletion, approximately 2.4 to 3 Mb as detected by FISH or chromosomal microarray. The deletion affects approximately 50 genes and 7 micro-RNAs [5••]. The size of the deletion remains unchanged when inherited from an affected parent. However, the phenotype can be widely variable, even within a family. Although smaller recurrent deletions that are half the size of the common deletion occur (1.5 Mb), a smaller size does not correspond with milder symptoms, making genotype-phenotype correlations difficult. Most 22q11 deletions occur as de novo events, with approximately 10% inherited from an affected parent.

22q11.2 Deletion Syndrome Clinical Findings

A deletion of chromosome 22q11.2 has been identified in the majority of patients with the classically termed conditions DiGeorge, velocardiofacial (VCFS), and conotruncal anomaly face (CTAF) syndromes, leading to the realization that these clinical entities all reflect features of the same genomic disorder [5••, 9]. The list of findings associated with the 22q11.2 deletion syndrome is extensive and varies by patient. Estimates indicate that the microdeletion occurs in approximately 1 in 1000 fetuses [10]. This disorder is the most common microdeletion syndrome occurring in humans and is a significant health concern in the general population.

The core clinical phenotype of 22q11.2 deletion syndrome (22q11.2DS) is still characterized by a conotruncal cardiac anomaly, aplasia/hypoplasia of the thymus and parathyroid glands. The majority of patients with a deletion can receive a diagnosis as newborns or infants presenting with significant cardiovascular malformations, including interrupted aortic arch type B, truncus arteriosus, or tetralogy of Fallot, along with functional T cell abnormalities and hypocalcemia. In addition, facial dysmorphia may be present, including hooded eyelids, hypertelorism, overfolded ears, bulbous nasal tip, a small mouth, and micrognathia. Since the initial reports, the spectrum of associated clinical features has been expanded to include anomalies such as palate defects, vascular rings, feeding and swallowing dysfunction, gastroesophageal reflux,

renal agenesis, and hypospadias [11•]. Before advances in the medical and surgical management of children with complex congenital cardiac disease and immune deficiencies, this disorder was associated with significant morbidity and mortality. Today, it is typically managed as a chronic condition.

Developmental delays or learning disabilities are seen in most patients with the 22q11.2 deletion syndrome, and a wide range of developmental and behavioral findings has been observed in young children. In the preschool years, affected children were most commonly found to be hypotonic and developmentally delayed with language and speech difficulties. Severe or profound retardation was not seen, and one third of patients functioned within the average range [11•]. In addition, behavioral and psychiatric disorders have been reported in many patients, ranging from anxiety and depression to psychosis and schizophrenia. The association with psychiatric disorders is a particularly active area of basic and translational research.

Immunologic Manifestations

22q11.2 deletion syndrome is classically associated with various degrees of T cell lymphopenia and dysfunction due to aplasia or hypoplasia of the thymus, which arises from the third and fourth arch structures of the pharyngeal apparatus during embryonic development [12]. As T lymphoid cells that have egressed from the bone marrow require interaction with thymic stromal cells for proper maturation, abnormalities in thymic structure can have life-long implications in the immune system. The majority of patients with 22q11 deletion syndrome (22q11DS) have thymic insufficiency resulting in a clinically heterogeneous picture ranging from severe T cell lymphopenia to normal or near-normal T cell counts. Although the severity of immunodeficiency is correlated with the extent of thymic hypoplasia, children who appear to have absent or small thymic shadows on imaging can still have normal T cell numbers due to ectopic thymic tissue nested within the mediastinum [13••].

Approximately 75% of patients with 22q11DS have derangements in the immune system [14] and hypoparathyroidism is correlated with clinically apparent T cell lymphopenia [15]. Those with more profound lymphopenia may have increased susceptibility to pathogens associated with T cell deficiency, such as *Candida albicans* and viral infections, although this is not the typical presentation. Most patients who are symptomatic experience increased sinopulmonary infections, which may be, in part, attributed to other 22q11.2DS associated co-morbidities such as velopharyngeal insufficiency, eustachian tube dysfunction, and gastroesophageal reflux. Even those with initially normal T cell numbers can develop an exhausted T cell phenotype in adulthood due to the homeostatic proliferation of existing mature T cells rather than newly derived thymic T cells possessing new T cell receptor specificities [13••, 14]. Despite this early T cell senescence, opportunistic infections are rare and viral respiratory infections are the most common type of infection [13••]. Complete athymia is found in about 1.5% of patients with 22q11DS and results in a clinical picture analogous to severe combined immune deficiency (SCID) requiring early intervention [16].

The immune deficiency associated with 22q11DS also affects the humoral arm of the immune system. Hypogammaglobulinemia and poor vaccine-specific antibody responses are frequently described in patients with 22q11DS with a small percentage of patients requiring prophylactic antibiotics and/or immunoglobulin replacement [17–20]. B cell production and differentiation appears to be normal except for a deficit in switched memory B cells and decreased somatic hypermutation. This is thought to be the result of aberrant T cell help rather than B cell exhaustion evidenced by normal bone marrow B cell output as measured by kappa-deleting recombination excision circles (KRECs) [21].

Similar to other diseases with T cell dysfunction, autoimmunity is increased in patients with 22q11DS [13••]. This frequently manifests as juvenile idiopathic arthritis, autoimmune cytopenias, and hyper-hypothyroidism [12]. Atopic diseases, including asthma, rhinitis, eczema, food allergy, and drug allergy, also require close monitoring since uncontrolled atopy can contribute to worsened respiratory infections. The immunologic consequences of 22q11DS are summarized in Fig. 1.

The immune evaluation of individuals suspected to have 22q11DS should include a complete blood count with differential, T and B cell enumeration, quantitative immunoglobulins, and antibody titers to vaccines (if appropriate). While neonatal diagnosis has historically relied on molecular cytogenetic testing and recognition of the phenotypic features associated with the syndrome, the inclusion of T cell receptor excision circles (TRECs) in the newborn screening (NBS) panel for SCID now allows for the early identification of 22q11DS patients with profound T cell lymphopenia. In a review of over 3 million TREC results from the California NBS program, 22q11DS was responsible for 19% of neonates with non-SCID T cell lymphopenia [22]. As of September 2017, all 50 states, the District of Columbia, the Navajo population in Arizona, and Puerto Rico are either actively screening or committed to full implementation, providing another avenue by which patients with T cell lymphopenia due to 22q11DS can be diagnosed. TREC screening will not detect cases in which T cell counts are within normal limits, but it can increase the likelihood of early diagnosis for those with more profound symptoms and allow for timely intervention and avoidance of protracted diagnostic evaluations which can take years, particularly in those with more mild cardiac or craniofacial characteristics [23]. There is a strong likelihood of seeing many more infants with 22q11DS diagnosed early in infancy due to newborn screening using the TREC assay, and these patients may initially present to an immunologist.

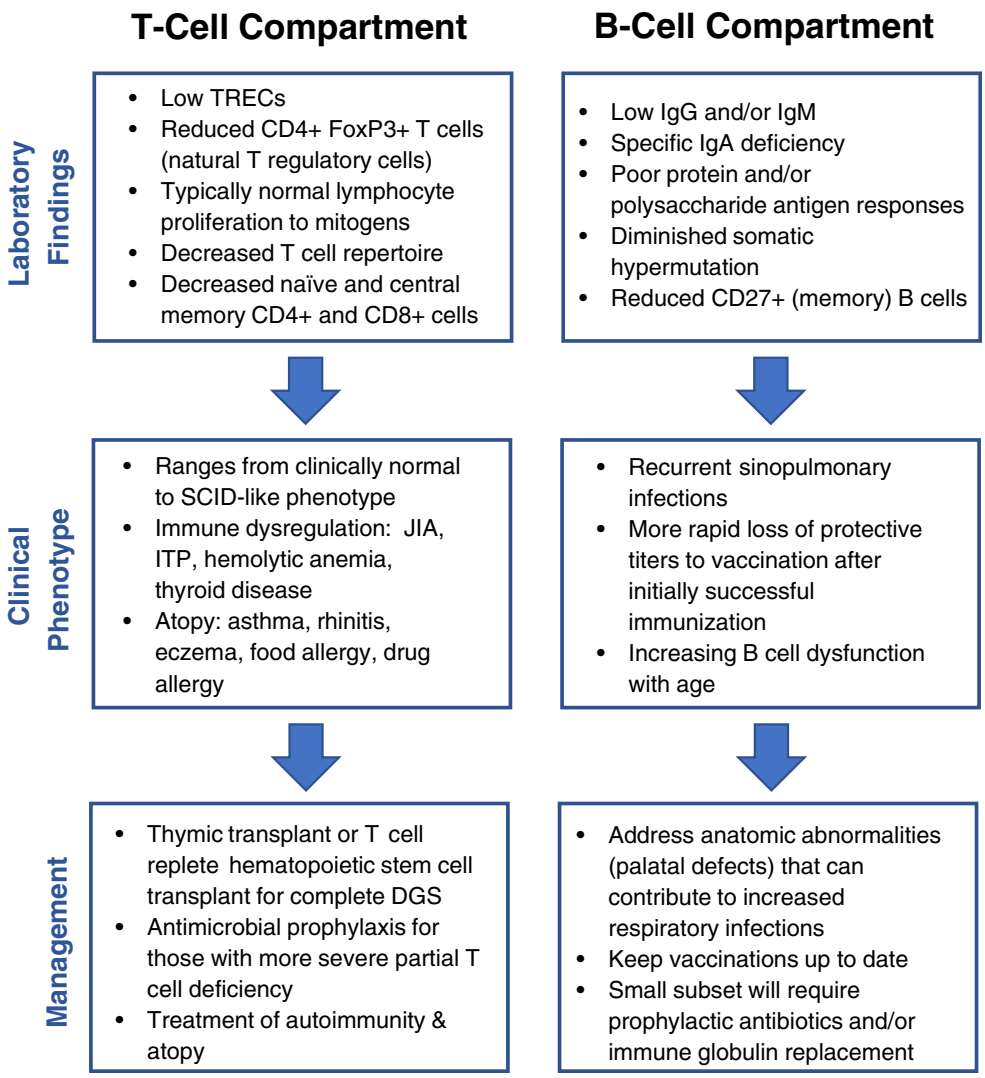

Fig. 1 A schematic representing a diagnostic and management approach to patients with 22q11 deletion syndrome

In patients who have evidence of T cell lymphopenia, more advanced studies such as in vitro T cell proliferation responses to mitogens, measurement of CD45RA+ naïve T cells, and characterization of T cell receptor repertoire by flow cytometry should be evaluated. Although clinical practice guidelines for the immune system in 22q11DS have yet to be established, T cell counts, immunoglobulin levels, and vaccine-specific antibody titers should be followed every 2–5 years depending on the frequency of infections [13••]. Prophylactic antibiotics and/or immunoglobulin replacement can be given for those with recurrent infections and hypogammaglobulinemia or poor specific antibody responses.

Hematopoietic Stem Cell Transplant, Thymic Transplant, and Outcomes

In individuals with athymia, two possible treatment approaches are either T cell-replete hematopoietic stem cell transplantation (HSCT) or thymus transplantation. Although the first option would result in engraftment of only post-thymic T cells, there are multiple reports of this being successful [24]. In contrast to other primary immune deficiencies in which engraftment of hematopoietic stem cells is the goal, this approach involves the adoptive transfer of mature T cells, which have already undergone positive and negative selection in the donor thymus and therefore should provide T cell function if there is sufficient T cell receptor diversity. Many of these patients were transplanted without conditioning and achieved some level of persistent T cell chimerism composed largely of the memory T cell phenotype at long-term follow-up [24]. As would be expected with T cell-replete transplants, graft-versus-host disease can be a complication of HSCT in 22q11 deletion syndrome. Several patients have also received adoptive transfer of peripheral blood mononuclear cells as well as transplantation of cord blood [25]. Since cord blood contains fewer mature and memory T cells, the clinical efficacy of this approach requires further evaluation.

Alternatively, thymus transplantation is a therapeutic option that has the potential for more complete T cell reconstitution in 22q11DS. In contrast to HSCT, successful thymic engraftment allows for the production of naïve T cells that possess a broad TCR repertoire [26•]. In the USA, transplants are performed at a single center, where thymic tissues are collected as discarded tissues from infants undergoing cardiac surgery [26•]. Combining results of thymic transplant in patients with DiGeorge syndrome (22q11DS) and other underlying etiologies of the clinical DiGeorge anomaly (CHARGE, infants of diabetic mothers), development of naïve T cells can be achieved, although generally below the 10th percentile for age [26•]. Restoration of T cell proliferative responses to mitogens and B cell vaccine responses have also been reported [27]. There are few adverse events associated with the procedure itself and the survival rate of thymic transplant is similar in those with 22q11DS and other forms of DiGeorge anomaly [28], but the most common clinical complication following thymic transplantation is autoimmune disease [16, 26•]. Reported manifestations of autoimmunity include Hashimoto thyroiditis, cytopenias, nephrotic syndrome, alopecia totalis, autoimmune hepatitis, skin granulomas, and enteritis/colitis [26•].

The outcomes of the European experience with thymic transplants in patients with a clinical diagnosis of DiGeorge anomaly (and a range of underlying etiologies) have been similar to those in the USA, with similar rates of T cell reconstitution but with frequent autoimmune complications [16]. Focusing on outcomes of just those with 22q11 deletions, three of six patients died, two from pre-existing viral infections and one from treatment-refractory ITP. Two of the three survivors remained on immunoglobulin for 21 to 80 months post-transplant, and all three had autoimmune complications, including colitis, cytopenia, thyroiditis, and transaminitis. T cell reconstitution generally did not reach normal numbers for age, but there were gradual increases in naïve T cells, which persisted at a low, but steady level. In all, studies of thymic transplantation thus far have demonstrated the potential for clinically relevant levels of immune reconstitution with thymic transplantion, but further work is ongoing to better understand and hopefully prevent the autoimmune consequences of the procedure.

Genetic Counseling in 22q11

The 22q11 deletion syndrome most often occurs as a de novo event, not inherited from a parent, with an affected patient having a 50% risk of transmitting the deletion to each of their offspring in an autosomal dominant manner. There is wide inter- and intrafamilial variability in clinical features and individuals in the same family with the same genotype may have different organs systems affected with a range of severity.

While the majority of patients have a similar 2.5–3.0 MB-sized deletion, a subset of patients have a smaller "nested" or central deletion whose breakpoints are contained within the larger typically deleted region [8]. Patients with overlapping features can also have deletions immediately adjacent and distal to the typically region of chromosome 22q11.2, known as distal deletions. A significant percentage of these central and distal deletions are not detectable by the standard probes used for FISH analysis and an alternative method such as chromosome microarray may be needed to identify the deletion.

For newly diagnosed patients, it is prudent to obtain a thorough family history with specific attention to conditions suspicious for the phenotype which may have gone undiagnosed or under-recognized such as a history of recurrent infection, psychiatric diagnoses, learning disabilities, a history of speech delay, and hearing loss along with other related findings such as a congenital heart defect and/or a cleft palate with or without lip involvement. Approximately 7–10% of cases are inherited from an affected parent, often undiagnosed [11•]. It is recommended to obtain parental genetic studies in newly diagnosed individuals, as parents of an affected child may have mild clinical features and in fact carry the deletion and also be affected. Reproductive genetic counseling is beneficial for affected adults who want to discuss the availability of genetic diagnosis and screening options throughout pregnancy, understanding the challenges presented when these patients have significant learning disabilities or psychiatric issues. Currently, diagnostic testing for the 22q11 deletion is available in the first trimester with chorionic villus sampling and in the second trimester with amniocentesis. A screening protocol may include noninvasive prenatal screening (NIPS) and/or targeted ultrasounds; however, these are not considered diagnostic tests and would require a follow-up sample from CVS or amniocentesis for diagnosis. Preimplantation genetic diagnosis (PGD) with in vitro fertilization also may be available for affected patients.

If both biological parents undergo genetic testing with negative results, then the child's deletion would be considered a de novo event in the family. Recurrence risk for these parents is quoted at 1–3% due to the risk of germline mosaicism. Advances in the care of young adults with congenital heart defects and immune dysfunction have allowed more infants with a 22q11 deletion to grow to adulthood and consider having children. Therefore, reproductive genetic counseling should be offered to address recurrence risk and discuss genetic counseling in pregnancy for these patients.

Conclusions

In the 50 years since DiGeorge presented patients with a recurrent triad of congenital heart defects, hypoparathyroidism, and structural thymic defects, extensive basic and clinical research has been focused on its underlying cause, early

identification of patients and best practices in clinical management. The chromosome 22q11 deletion syndrome is now known as the underlying genetic etiology for the vast majority of patients with clinical DiGeorge syndrome and this multisystem disorder is the most frequently encountered microdeletion syndrome in humans. Advances in congenital cardiac surgery, treatment of immune dysfunction, and other interventions have turned this disorder, once frequently fatal in infancy, into a chronic condition with patients surviving well into adulthood. There is a wide spectrum of immune impairments experienced by these patients, requiring the immunologist to play a central role in their multidisciplinary management.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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