Review

Endocrine manifestations in DiGeorge and other microdeletion syndromes related to 22q11.2

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INTRODUCTION

Microdeletions, translocations or other rearrangements of chromosomal region 22q11.2 have been reported in association with >80 different birth defects and malformations occurring in many combinations and with widely differing severity.[1] Furthermore, a tendency to report atypical cases and ascertainment of published series according to the author's speciality have resulted in the same deletion being linked to a heterogeneous group of disorders that share a common genetic basis, including the DiGeorge (DGS), velocardiofacial (or Shprintzen) (VCFS), and conotruncal anomaly face (CTAF) syndromes. Ninety percent of patients with DGS, 68% of VCFS, and 30% of CTAF patients are known to carry this deletion.[2-4] The prevalence of DGS/VCFS is approximately 1:4.000[5] and they represent one of the most frequent genetic diseases, taking into consideration that this figure may be

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underestimated because of the rate of perinatal deaths observed in many cases with a severe congenital heart defect. The acronym "CATCH 22" (Cardiac anomalies, Abnormal face, Thymic hypoplasia, Cleft palate, and Hypocalcaemia) resulting from 22q11 deletions has also been proposed to describe the phenotype. Deletions on the short arm of chromosome 10 p13p14 are also associated with a DGS-like phenotype but are much less common than 22q11.2 deletions, occurring with an estimated frequency of 1 in 200,000 live births.[6]

CLINICAL PHENOTYPE

The cardinal symptoms and clinical features of DGS/VCFS with 22q11.2 deletion are conotruncal heart defect with high morbidity and mortality, cellular immunodeficiency due to thymus and parathyroid hypo-plasia or aplasia, hypocalcemia, velopharyngeal insufficiency, and typical dysmorphic faces which include prominent nose, broad nasal root, narrow palpebral fissures, hypertelorism, retro-micrognathia and low-set ears.[7,8] In at least 10% of cases examined, an increased frequency of psychiatric diseases, such as schizophrenia or bipolar disorders, has also been observed after longterm follow-up of patients seen initially as infants or young children.[9] It is likely that those patients with a clustering of abnormalities, such as microcephaly, developmental delay, cleft palate, velopharyngeal insufficiency, and relatively mild heart defects, come to be diagnosed as VCFS, whereas those with more caudal anomalies (thymic and parathyroid hypoplasia, se-

vere heart defects with right-sided aortic arches) are diagnosed as DGS.[10]

Cardiac malformations, speech delay, and immunodeficiency are the most common characteristics, although no single prominent of feature is overwhelmingly associated with the deletion 22q11.2.[7,11] None of the phenotypic features is pathognomonic for the deletion, the presence of which does not predict end-organ effects or severity with any certainty.[12] Nevertheless, a high index of suspicion is warranted for children presenting with the classic manifestations of DGS/VCFS, as well as for patients with a single common manifestation and one or more uncommon ones.[13] Most affected patients fall near the center of the distribution of severity so that the largest number of cases, which resemble each other, tend to fall near the mode of that distribution.[7]

Patients reported so far with the deletion at 10p13p14 exhibit at least one of the classic features of DGS (cardiac defect, hypocalcemia, and/or immune defect) and they share the following features with DCS/VCFS: cardiac defects, transient hypoparathyroidism/hypocalcemia, T-cell deficiencies, facial anomalies such as low-set and small ears, micrognathia and facial clefts, hypertelorism, short nose with anteverted nares, abnormally shaped skull, microcephaly, hand and foot abnormalities, genitourinary anomalies, hearing loss, and severe psychomotor retardation.[14-21] An update on the phenotypic manifestation of DGS/VCFS is given on two web sites, serving as excellent resources for families and caregivers (www.vcfsef.org, http://www.cbil. upenn.edu/VCFS/22qandyou/).

MOLECULAR GENETICS OF DIGEORGE SYNDROME CAUSED BY A 22q11.2 DELETION

DGS/VCFS phenotypes represent the expression of developmental disturbances of neural crest during the embryogenesis of the third and fourth pharyngeal pouches and are attributed to the haploinsuffiency of one or more of the genes located in the chromosomal region 22q11.2.[22,23]

Most patients have an interstitial deletion of ~3 Mb, the typically deleted region (TDR).[24] In this region the estimated number of genes is over 100 and since no one gene has been definitely demonstrat-

ed to play any specific role, the DCS/CVFS are considered to be contiguous genes syndromes.[16,25-27]

Candidate genes likely to be responsible for the DGS phenotype are: the ubiquitinfusion-degradation-l-like (*UFDIL*) gene,[25-29] the *TBX1 gene,*[25-31] and the platelet glycoprotein gene, *GP1b,*[13] while other genes may also play a role in the behavioral aspects of the syndrome.[32,33] The study by Taddei et al[34] in a mouse model supported the idea that background genes can influence the phenotypic expression, while it also provided a potential explanation for the diversity seen within single families.

The 22q11.2 deletion is inherited in 5-10% of cases, but the observation of phenotypic differences among members of the same family carrying an identical deletion is indicative of a more complicated molecular genetic basis. It has also been shown that the clinical severity is not related to the length of the deletion.[32,35] Moreover, during the last 5 years a number of reports describing DGS or VCFS-like features in patients with atypical deletions have appeared in the literature, making it difficult to reach an overall conclusion concerning the position of critical genes.[36-39]

The possible mechanisms of 22q11.2 deletion are reviewed in the excellent paper by Scambler[1]. In parents of children with the above deletion, recombination studies detected an excess of meiotic events within 22q11, suggesting that unequal crossing over may occur in the deleted region.[40-44]

Since FISH was implemented as a laboratory test for DGS and VCFS by the disclosure of two signals on chromosomes 22 in normal patients and one signal only when a deletion is present, the number of patients diagnosed has increased dramatically, including patients with mild to severe phenotypes.[45] In a series of 193 Greek patients referred for DGS/VCFS to the Department of Medical Genetics of Athens University, a deletion was detected by FISH in 17 (12.2%), confirming the clinical diagnosis.[46]

There are also reports in the literature of patients with DGS/CFS phenotypes but without a 22q11.2 deletion[1]. It is possible that the deletion-negative patients have smaller chromosomal deletions that could not be detected by FISH or have a point mu-

tation in a critical gene within the TDR critical region of DGS/VCFS.[47]

MOLECULAR GENETICS OF DIGEORGE SYNDROME CAUSED BY A 10p13p14 DELETION

As already mentioned, deletions on the short arm of chromosome 10 p13p14 are also associated with a DGS-like phenotype but are much less common.[6] This deletion was first reported by Elliot et al in 1970[48] and a decade later it was associated with DGS anomalies.[49-51]

It has been suggested that there are two non-overlapping haploinsufficiency regions on 10p which contribute to the DCS/VCFS phenotype. Lichtner et al[18] revealed hemizygosity of the proximal region, designated DGCR2, which can cause cardiac defect and T cell deficiency, while hemizygosity of the distal region, designated HDR1, can cause hypoparathyroidism and, in addition, sensorineural deafness and renal dysplasia/insufficiency or a subset of this triad.

To exclude abnormalities within the 10p13p14 region, a FISH assay was designed.[6] Also, a dual-probe FISH assay, including test probes for both the DGS I and DGS II loci and centrometric probes specific for chromosomes 22 and 10 has been developed by Berend et al[6] and is especially helpful when the clinician requests a FISH test without a standard karyotype.

ENDOCRINE MANIFESTATIONS

The most frequent endocrine disorders associated with DGS/VCFS are short stature, hypocalcemia, thymic related immunodeficiency, and, less frequently, autoimmune and thyroid disorders.

GROWTH FAILURE

Short stature is a common problem associated with 22q11.2 microdeletion syndrome[52] and was originally reported in 30% of VCFS cases.[53] In a review of 120 patients by Goldberg et al,[20] analysis of growing children with VCFS showed their height to be below the 5th centile. However, among them only about 10% remained below the predicted height and

had true short stature. In the majority of cases the predicted height matched their target height, indicating that a component of the short stature may be caused by constitutional growth delay.

From European collaborative study by Ryan et al[7] growth data (sex, height, weight, head circumference) were available in 158 patients with 22q11.2 deletions. Growth retardation was common; 131/158 (83%) of patients had heights/weights below the 50th centile, and 57/158 (36%) were below the 3rd centile for either height or weight. In the same population, 46/120 (38%) of patients with congenital heart disease (CHD) were below the 3rd centile for either height or weight, as compared to 11/38 (29%) of patients without CHD (not statistically significant). Head circumference measurements were in agreement with those for height and weight. The observation that most babies were born within the normal size range, but 33/205 (16%) were below the 3rd and 147/205 (72%) were below the 50th centile, suggests an intrinsic problem causing growth retardation. In the same study, childhood measurements were frequently on a lower centile than birth weight, with 57/158 (36%) being< 3rd and 131/158 (83%) <50th centile. According to the authors, this may be related to feeding problems in the neonatal period, while recurrent infections were not considered to play a significant role. Congenital heart defect is one, but not the sole, explanation.

Growth hormone deficiency in patients with 22q11.2 deletion was reported by Weinzimer et al[52] in 4 cases. Growth hormone deficiency with abnormal pituitary anatomy has also been reported in some cases, with growth hormone therapy improving the patient´s final height.

In a summary of clinical findings of 250 patients undergoing an extensive multispecialty evaluation at the Children's Hospital of Philadelphia,[11] short stature was reported in 10-40% of patients, with growth hormone deficiency in some children who were significantly below the 5th percentile for height. In half of the patients with growth hormone deficiency, pituitary gland abnormalities were diagnosed by MRI. These patients had responded dramatically to growth hormone therapy with accelerated linear growth. It was also observed that short stature

was present independent of cardiac defects. The authors suggested that growth hormone deficiency, specifically low levels of insulin-like growth factor I and insulin-like growth factor binding protein, should be suspected in children with DGS/VCFS whose height or growth velocity is less than the 5th percentile.

More recently in the study of Brauner et al,[54] children with 22q11.2 deletion were at birth below - 2SD for weight in 22% of the cases and for length in 17%. Short stature later on was attributed to intrauterine growth retardation, feeding difficulties, or growth hormone deficiency, as suggested by low insulin-like-growth factor (IGF-I).

Finally, Choi et al[55] in a series of 61 patients with 22q11.2 microdeletion observed ten patients (16.4%) below the 3rd percentile in height, but the serum IGF-1 level was normal in nine and the serum IGFBP-3 levels were normal in all patients. No significant correlation was found between the severity of short stature and the serum IGF-1 and IGFBP-3 levels. In the same study, in 16/61 patients the weight at birth with a full-term gestation was below the 3rd percentile (26.2%), indicating intrauterine growth retardation. However, birth length data were not available in most patients; 7/16 patients showed progressive catch-up growth with time.

HYPOCALCEMIA - PARATHYROID DYSFUNCTION

It has been reported that hypocalcemia results from abnormal third and fourth pharyngeal pouch development, resulting in defective organogenesis or absence of the parathyroid glands.[56-58]

Parathyroid anomalies have been described as one of the typical findings in DGS, and hypocalcemia due to hypoparathyroidism is found in 70% of patients with the DGS/VCFS phenotype and in 40-60% of those with the 22q11.2 deletion.[28] It is noted that parathyroid function varies among patients and even in the same patient at different times. In most patients presented for clinical evaluation between birth and age 3 months with a variety of symptoms including seizures, tremors, and rigidity, serum measurements of total calcium ranged from 5.5 and 7.1 mg/dl.[20] Severe hypoparathyroidism in the neonate

almost always resolves spontaneously and completely, with eventual resolution and without subsequent symptoms or complications, because as the parathyroid glands hypertrophy, hypocalcemia generally improves over the first year of life.[13,21,59] Hypoparathyroidism with hypocalcemia may or may not recur later in life.[21,59]

Creig et al[21] reported transient congenital hypoparathyroidism (TCHP), with spontaneous resolution in infancy and subsequent recurrence in childhood in three patients with (VCFS). The neonatal hypocalcemia in these patients and in another five reported previously, with resolution and later recurrence, were characterized by severe hypocalcemia at onset. In this group as a whole, the majority had seizures (5/8), required intravenous treatment with calcium (5/8), and needed prolonged therapy. The authors suggested that in order to distinguish hypocalcemic infants with TCHP from the majority of infants with benign neonatal hypocalcemia, the demonstration of low levels of PTH or of elevated phosphate levels is helpful. Furthermore, neonates with severe hypocalcemia and apparent hypoparathyroidism should receive further evaluation for adequacy of parathyroid secretion and should undergo examination for specific features of VCFS, since these features may not be easily apparent. Infants with resolved TCHP need continuous follow-up of parathyroid function, genetic analysis, and examination for anomalies associated with chromosome 22q11 deletion.[21]

Prolonged mild hypocalcemia may be unrecognized for a long time, but even mild hypocalcemia may be clinically significant, and the risk is high for arrhythmia, syncope, or sudden death, especially in the adolescent or adult who may have repaired conotruncal cardiac defect.[28] Even mild hypocalcemia evokes a rapid and sustained increase in intact parathyroid hormone (iPTH) levels in infants, children, and adults. Results from a previous study by Cuneo et al[47] demonstrated that in children with Conotructal Cardiac Defects (CTCD) who were normocalcemic at rest, 50% had a reduced ability to secrete iPTH in response to evoked hypocalcemia, compared with a control population of children with atrial septal defect (ASD). The authors called this response latent hypoparathyroidism, implying

a reduced iPTH secretory reserve.

Latent hypoparathyroidism, defined as normocalcemia with decreased parathyroid hormone reserve in response to hypocalcemic stress, is not a well known manifestation of the 22q11.2 deletion syndrome.[28] Latent hypoparathyroidism can progress to overt hypocalcemic hypoparathyroidism, especially during stressful conditions.[47] The identification of one patient with hypocalcemia at the age of 15 years emphasizes the need for continuous follow-up of patients with VCFS throughout life, especially during times of stress.[20]

The parathyroid function and calcium status were recorded by Ryan et al[7] in a cohort of 340 patients; 203/340 (60%) had been hypocalcemic and this was generally associated with symptoms in the neonatal period. However, several patients presented with hypocalcemia in childhood and one patient presented at the age of 18 years. Of the 108/203 hypocalcemic patients whose seizures history was documented, 42/108 (39%) had seizures secondary to hypocalcemia and the majority of them responded well to calcium supplements, with cessation of seizures. The hypocalcemia resolved in 45/64 (70%) patients and the remainder continued on calcium supplements, but it was not known if parathyroid function had been reassessed. The authors suggest that the calcium-parathyroid hormone axis (ionized calcium plus intact parathyroid hormone levels) should be evaluated regularly in patients with 22q11.2 deletion, while the maintenance therapy for hypocalcemia should include 1,25-dihydroxy vitamin D with or without oral calcium to maintain serum ionized calcium in the low-normal range.

In a review of chromosome 22q11.2 deletion syndrome (DGS/VCFS) by Perez and Sullivan,[13] it was emphasized that neonatal hypocalcemia is one of the strongest predictors of a chromosome 22q11.2 deletion and is present in 17-60% of patients, depending on the definition used. Few older patients require ongoing calcium supplementation, but it has become increasingly clear that hypocalcemia can develop in older age, presenting with new onset of tetany or seizures in adults with previously undiagnosed disease.[60,61] It is also known that hypocalcemia can be unmasked in adults under stress, because of acute medical conditions or trauma. This suggests that primary hypocalcemia at any age should be considered a risk for patients with this deletion.[13]

According to a recent report by Brauner et al in 2003,[54] hypocalcemia occurred in 74% of cases with 22q11.2 deletion when blood calcium concentrations were measured twice during the first 15 days of life, and in 49-60% of patients during childhood, verifying that hypocalcemia is more frequent in the neonatal period. In the same study a 22q11.2 deletion was found in 10 of 14 patients with hypoparathyroidism.

THYMIC RELATED IMMUNODEFICIENCY AND AUTOIMMUNE ENDOCRINE DISORDERS

The original description of the syndrome by DiGeorge in 1968[62] included a child with hypoparathyroidism and recurrent infections as well as the necropsy findings of three cases with absent thymus and parathyroid glands. A year ago DiGeorge et al reported four athymic infants and in one instance correctly diagnosed the thymic aplasia postmortem.[63] Although absence of thymus is considered a major feature of the syndrome, in a large collaborative European study in 1997 only 3 out of 263 DGS/VCFS patients with complete data on immune function had severe immunodeficiency.[7] Even in cases in which the thymus was absent or the laboratory results were abnormal, clinically significant immunological problems were uncommon. On the other hand, immunodeficiency was reported in 40-93% of people with the 22q11.2 deletion.[11,64,65]

People with DGS/VCFS phenotype and cardiac detects have been observed with absent or hypoplastic thymus at the time of surgery. Estimates of thymic tissue have been made by transthoracic echocardiography in children with conontruncal cardiac defects. A hypoplactic thymus may increase the likelihood that a deletion may be present. Children, however, with longstanding cardiac disease or heart failure often have a small thymus which predicts present or future immune disorder.[28] The observation of absent or hypoplastic thymus at the time of cardiac surgery is not infrequent in children with DGS/VCFS phenotype and cardiac defects.

Cell mediated immune deficiency is expected, especially in patients with the DGS phenotype, but disorders of humoral immunity also occur.[28] As to the severity of immunodeficiency, most children have a mild form characterized by low absolute T-cell numbers and a small, histologically normal thymus, but normal or near normal T-cell function. At the other end of the spectrum, immunodeficiency may be severe in some patients, characterized by thymic aplasia and absent T-cells. Severely affected people require aggressive immunodeficiency treatment, and they may even need thymic transplantation. The usual clinical picture in younger patients is susceptibility to upper respiratory infections, while older children have fewer infections and increased T-cell numbers and function. Patients suffer from prolonged viral infections and have frequent bacterial superinfections of the upper and lower respiratory tract. The infections are also seen in DGS/VCFS with normal T-cell numbers, suggesting that anatomy, reflux, allergies, cardiac disease, and poor nutrition contribute to the recurrent infections. Of the patients who have a mild to moderate decrease in T-cell production, the absolute T-cell numbers are not predictive of infections. Interestingly, among the few known adults, approximately 25% have recurrent infections.

The condition is often intensified by the co-existence of velopharyngeal insufficiency and other palate abnormalities.[13]

In our series of 17 patients with a confirmed deletion of 22q11.2, lymphocyte subpolulation disturbances were detected in 6 children (47%) with a mild clinical picture, and only one required prolonged medical treatment with intravenous gamma globulin administration.[46] It is interesting that one of our patients with a 22q11.2 deletion, but without neonatal immunological problems, developed lymphoma at the age of 15 years. To the best of our knowledge, this is the first case of DGS with hematologic malignancy.[46]

The immune status of people with the 22q11.2 deletion should be ascertained when the diagnosis is made by measurements of T and B-cell subsets from peripheral blood lymphocytes and by in vitro lymphoproliferative assay of T- cell function. Man-

agement of the immunodeficiency in DGS/VCFS is problematic. The use of a fully matched sibling bone marrow transplant or a thymic transplant is required for the profoundly immunodeficient patient.[13] The broad spectrum of immunodeficiency in chromosome 22q11.2 deletion syndrome makes it difficult to counsel patients and families regarding the morbidity or longterm consequences.[12]

The literature is consistent with the theory that the 22q11.2 microdeletion syndrome is associated with a predisposition to autoimmune disorders, which contributes to the extremely variable phenotypes of affected patients.[66]

Antibody production is generally normal, although IgA deficiency is increased in patients with the deletion and this may predispose patients to autoimmune disorders.[12,13] Autoimmune disease is seen in approximately 9% of all patients with the deletion. No one specific autoimmune disease is seen in this syndrome, but the risk of all autoimmune disease seems to be increased.

Autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, thyroiditis, type 1 diabetes mellitus, and juvenile rheumatoid arthritis have been associated with 22q11.2 microdeletion syndrome. Davies et al in 2001[67] postulated that hemideletion of TBX1 gene could result in premature thymic apoptosis and subsequent qualitative defect in immunological tolerance, thus predisposing to autoimmunity. T-cell defects due to absent or hypoplastic thymus gland can also result in defective cellular immunity. The defects of cellular immunity in 22q11.2 microdeletion patients may predispose to the development of immune dysregulation and autoimmune disorders. However, most of these patients have apparently clinically non-significant T-cell defects and clinical immunodeficiency, or both. Juvenile rheumatoid arthritis is statistically the most common autoimmune disease in children with the deletion. It appears to be more frequent in the subset of patients who have IgA deficiency.

DIABETES MELLITUS

Diabetes has been described, as has autoimmune thyroid disease, in a substantial subset of patients.

Elder et al[68] described a 9-year old boy with clinical findings consistent with velocardiofacial syndrome and a chromosome 22q11.2 deletion. He had the distinctive facial features, learning disabilities, short stature, and he presented with a history of glottic web, clubfoot, polyuria, polydipsia, weight loss, hyperglycemia, ketosis, serum insulin antibodies, and a low C-peptide level. The authors suggested that the presence of insulin antibodies in this patient indicate an autoimmune etiology for his diabetes mellitus type I, and suspected that the defects in immune regulation due to T-cell deficiency in chromosome 22q11.2 deletion syndrome may predispose to autoimmune disorders, including type I diabetes mellitus.

In the literature there are reports of six children born to diabetic mothers who, among many congenital anomalies, had cardiac defects, absent thymus, and parathyroid glands, as well as renal agenesis.[69-73] One of them was described as having apparent features of VCFS but without deletion in chromosome 22q11.2.[71] Elder et al (2001) speculate that it is possible that these diabetic mothers may have undetected microdeletions or some other mutation in the 22q11.2 region, which could have predisposed them, as well as their children, to 22q11.2 deletion syndrome and potentially diabetes development.

THYROID DYSFUNCTION

Thyroid hypoplasia was first reported in DGS by Robinson et al in 1975[74] but was not regarded as a component of VCFS until 1993, when Goldberg et al[20] observed one patient with hypothyroidism in a series of 120 patients with VCFS. This finding provided additional evidence of VCFS and DGS overlap. Subsequently, hypothyroidism (HP) was reported in more patients with the DGS/VCFS phenotype and 22q11.2 deletions.[11,71,73,75] In the study of Adachi et al out of 14 children diagnosed as HP, 10 (aged 9 days to 13 years) showed del 22q11.2.

With regards to autoimmune thyroid disease, in 2005 two patients were described, out of a series of 61 with 22q11.2 microdeletion, were described one with Graves' disease and one with Hashimoto thyroiditis , an incidence (3.3%) higher than that of the general population and with an earlier age of on-

set.[55] The 9-year old female with Graves' disease was detected because of abnormal thyroid function at the age of 40 months (TSH <0.05 µU/ml, free T_4 8,1 ng/dl, TSH receptor antibody 96,5%) and was treated with methimazol. The other patient, a 12-year old female with Hashimoto thyroiditis, who presented with goiter at the age of 10, was diagnosed due to elevated TSH (13.7µu/ml) and thyroid autoantibody levels, and since then has been treated with sodium L-thyroxine. The authors speculate that in these patients concurrence of autoimmune thyroid disorders with DGS/VCFS was not a chance association.

There are two previous reports of Graves' disease in patients with 22q11.2 deletion. Kawamura et al[76] reported an 18-year old female with partial phenotype of DGS, and Kawame et al[66] reported four females and one male diagnosed between the ages of 27 months and 16 years, when elevated serum levels of the thyroid hormones were detected, in association with suppressed thyroid-stimulating hormone levels. TSH-receptor antibodies and other characteristic anti-thyroid antibodies, such as anti-thyroglobulin and anti-microsomal antibodies, were positive in 3/5 patients. The clinical presentations were typical of hyperthyroidism, but in addition one female infant had seizures.

The pathogenetic mechanism of Graves' disease is thought to involve a complex interaction between genetic predisposing factors and environmental triggering ones. None of the several candidate genes, including the TSH receptor gene for nonautoimmune hypertyroidism that have been associated with Graves' disease, is located in the 22q11.2 chromosomal region of DGS/VCFS. Kawame et al[66] hypothesized that the combination of T-cell dysfunction, genetic susceptibility, and appropriate environmental triggering factors can precipitate autoimmune disease in some patients with the 22q11.2 deletion syndrome. They also proposed that the association between the 22q11.2 deletion and the development of Graves' disease is not coincidental, taking into consideration the higher incidence of Graves' disease among patients with the 22q11.2 deletion syndrome evaluated at the Children's Hospital, Philadelphia (1 in 352) than in the general population (17.7 in 100,000): This figure is approximately 16

times higher than the one seen in the general population.

Although the prevalence and the natural history of thyroid dysfunction in DGS/VCFS are not well characterized, baseline thyroid-stimulating hormone and T4 levels are highly recommended, since hypothyroidism is a treatable cause of both short stature and learning disabilities.[28] Clinicians should also be aware of the possibility of Graves' disease in patients with a 22q11.2 deletion at any age and evaluation of thyroid hormone function is indicated in patients with the syndrome and suggestive features of hyperthyroidism.[66]

CONCLUSION

Despite our increased understanding of the clinical spectrum and molecular genetics of the 22q11.2 syndromes, questions about the contributing factors in the extremely variable phenotypes still remain. Phenotypically similar people have deletions on different chromosomes, or are cytogenetically normal. In the field of clinical endocrinology, there is concern about the natural history of endocrine abnormalities in this syndrome and increased awareness of this syndrome, facilitate the early recognition of the abnormality.

Regarding the clinical management of patients with 22q11.2 deletion, they should be monitored for their height, weight, and parathyroid function. GH secretion and plasma IGF-1 should be evaluated in those who do not show any catch-up growth after intrauterine growth restriction or who have an unexplained slow growth rate. Those with a low GH peak and/or IGF-I may need magnetic resonance imaging to detect pituitary abnormalities. Pituitary hypoplasia may suggest GH deficiency. Nutritional conditions should be optimized and, whenever possible, pharyngeal abnormalities should be carefully corrected. In addition, the blood concentrations of ionized and total calcium and of PTH should be regularly measured, particularly in the neonatal and pubertal periods and at surgery, while parents and patients should be informed about the signs of hypocalcemia: paresthesias, cramps, and or rigidity.[54]

In conclusion, an optimal wide-ranging program

for medical care, including not only cardiac and immunologic follow-up, cognitive, speech, language, and neuropsychiatric evaluation, but also endocrine perspectives, are needed in order to limit the disabilities of patients with DGS/VCFS.

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