DOI Number: 10.5958/0974-9357.2019.00008.4

Digeorge Syndrome – Chromosome 22q1l Deletion Syndrome: An Update and Review

Anushi Singh[1], Rekha Kumari[2]

[1]Asst. Prof , Chn Department, [2]Asst. Prof, OBG Department,
School of Nursing Science and Research, Sharda University

ABSTRACT

The DiGeorge Syndrome was first described in 1968 as a primary immunodeficiency resulting from the abnormal development of the third and fourth pharyngeal pouches during embryonic life. It is characterized by hypocalcemia due to hypoparathyroidism, heart defects, and thymic hypoplasia or aplasia. Its incidence is 1:3000 live births and, despite its high frequency, little is known about its natural history and progression. ←This is probably due to diagnostic difficulties and the great variety of names used to describe it, such as velocardiofacial, DiGeorge, and CATCH 22 Syndromes, as well as conotruncal facial anomaly. All represent the same genetic condition, chromosome 22q11.2 deletion, which might have several clinical expressions. To describe clinical and laboratorial data and phenotypic characteristics of patients with DiGeorge Syndrome. Patients underwent standard clinical and epidemiological protocol and tests to detect heart diseases, facial abnormalities, dimorphisms, neurological or behavioral disorders, recurrent infections and other comorbidities.

Keywords - *DiGeorge Syndrome, velocardiofacial, CATCH 22 Syndromes, conotruncal facial anomaly*

INTRODUCTION

DiGeorge syndrome (DGS) is one of a group of phenotypically similar disorders—including velocardiofacial syndrome (VCFS, or Shprintzen syndrome) and conotruncal anomaly face (CTAF) syndrome—that share a microdeletion of chromosome 22q11.2, a region known as the DGS critical region[1]. Cytogenetic and molecular studies have contributed greatly to our understanding of the genetic basis of these disorders. These studies suggest that one or more genes in this region of chromosome 22 play a major role in cardiac and craniofacial development and other derivatives of the third and fourth pharyngeal pouches, including the thymus and parathyroid glands. During the past several years there has been a tremendous effort by several groups of investigators to construct physical and transcription maps of this region to identify candidate genes. Within the next several years, we can expect that additional genes within 22q11 will be identified and that we will have a better understanding of their function and role in the development of the complex and variable phenotype of the 22q11 deletion syndrome.[2]

Corresponding author:
Anushi Singh
Asst. Prof, Chn Department, School Of Nursing Science And Research, Sharda University
E-mail: anushi.singh@sharda.ac.in

HISTORY

Genes are made up of a chemical called DNA and are housed on larger structures called chromosomes. Most people have 23 pairs of chromosomes (46 total), with one of each pair coming from the mother and the other from the father. Chromosomes are number 1 through 22; the 23rd pair are called sex chromosomes because they determine a person's sex (male or female). The chromosomes are found in every cell in the body.[3]

In 1981, Dr. de la Chapelle in France, and in 1982, Richard Kelley, M.D., along with Elaine Zackai, M.D. and Beverly Emanuel, Ph.D. at the Children's Hospital of Philadelphia in the U.S.A., found that

patients with DiGeorge syndrome had a rearrangement of chromosome 22 which caused them to be missing a very small piece of chromosomal material on the long arm (q11.2) of chromosome 22. This rearrangement was able to be seen under the microscope. This piece of information is important, as you will see when you read on, because most 22q11.2 deletions are not seen under the microscope because they are too small.[3]

Over the years, Dr. Emanuel's group at the Children's Hospital of Philadelphia worked very hard to establish the fact that 25% of patients with DiGeorge syndrome had a visible deletion of material on chromosome 22 when they looked under the microscope. But they were still puzzled about the other 75% of patients with DiGeorge syndrome who did not have a visible deletion. In 1991, Deborah Driscoll, M.D., a member of Dr. Emanuel's laboratory group, detected a submicroscopic deletion of chromosome 22q11.2 in the majority of patients with DiGeorge syndrome using special "molecular" tests. This meant that although you could not see the material under the microscope, you could prove that the piece was absent by using a special DNA test called FISH (fluorescence in situ hybridization). This test works like a lock and key. The person in the laboratory has the key which lights up (fluoresces) if it finds its matching lock in the chromosomes. If the lock is missing from one of the pair of chromosomes 22s, only one chromosome 22 will light up in the area in question (q11.2), confirming that the patient is missing material on chromosome 22.[4]

The majority of patients who had a 22q11.2 deletion, which caused their DiGeorge syndrome, did not have an affected parent, therefore, the change in their chromosome 22 was a "new mutation" in them. This was and still is important information for families, because, if the parents' chromosomes are normal, then the chance of recurrence in a future pregnancy is quite low. About 10% of the time, a parent is also affected with some medical problem like a heart defect and also has the 22q11.2 deletion. If the deletion is present, then that individual has a 50% chance of passing on the chromosome 22 with the deletion to his or her children. The chance of having more than one child affected when the parent has the deletion is random (like the chance of flipping a coin twice in a row and finding "heads" twice in a row). When a child receives the chromosome 22 with the deletion, the medical problems can be quite variable. For example, from a very mild heart problem to a very severe heart problem, or no heart problem at all.[2]

DEFINITION OF DI GEORGE SYNDROME

DiGeorge Syndrome (DGS) is a primary immunodeficiency, often but not always, characterized by cellular (T-cell) deficiency, characteristic facies, congenital heart disease and hypocalcemia. DGS is caused by abnormal formation of certain tissues during fetal development. During fetal development, various tissues and organs often arise from a single group of embryonic cells. Although the tissues and organs that ultimately develop from this group of embryonic cells may appear to be unrelated in the fully formed child, they do have a similar origin.[3]

Approximately 90% of patients with DGS have a small deletion in chromosome number 22 at position 22q11.2. Thus another name for this syndrome is the 22q11.2 deletion syndrome. Other names include velocardiofacial syndrome and conotruncal anomaly face syndrome.[5]

EPIDEMIOLOGY

22q11DS is the most common microdeletion syndrome in humans. However, population-based estimates of the incidence and prevalence of 22q11DS differ. Most studies reported a prevalence of one in every 4,000 newborns; however, reports range from one in 2,000 to one in 6,395.3,[12]Nevertheless, many researchers believe that this number is artificially low due to under-diagnosis. Consistent with this, familial occurrence is the most frequent cause of diagnosis in adults at some genetic centers.[10]

Male and female sexes are affected equally by 22q11DS. In addition, the deletion of 22q11.2 is more prevalent within certain ethnic groups. Specifically, 22q11DS occurs more frequently among Hispanics compared with Whites, African Americans, and Asians.[9]

Generally, >90% of DGS cases are de novo or novel deletions caused by a random occurrence during fetal development. An unaffected parent might then carry the deletion in his or her eggs or sperm, and the risk of recurrence is ~1%. However, it can also be inherited, and familial autosomal dominant recurrence is reported in ~8%–28% of patients in various series.[2] Some cases appear to have a vigorous diagnosis but no deletion; 35%–90% of patients with DGS and 80%–100%

of velocardiofacial syndrome patients have the 22q deletion.[12]

CLINICAL FEATURES

The variability in the clinical expression of del22 syndrome is extremely wide.[9] Classical features of del22 syndrome include CHD, velopharyngeal insufficiency or cleft palate, facial anomalies, speech and learning disabilities, neonatal hypocalcemia, and T-cell immune deficit. Nevertheless, the spectrum of anomalies associated with del22 is becoming wider and wider.[2] Inter-individual variability in del22 phenotype is characteristic, since subjects with full-blown clinical expression of the syndrome as well as mildly affected individuals can be found. The main clinical features of Del22 syndrome and their occurrence in series of 165 patients are listed in[6]

Table 1- Main clinical features of Del22 syndrome and their occurrence in this series

Clinical finding	Affected individuals	%
Facial anomalies	165/165	100%
Congenital heart defect	136/165	82%
Speech / Learning difficulties	132/165	80%
Neonatal hypocalcemia	121/165	73%
T-cell deficiency	97/141	69%
Skeletal anomalies	52/165	32%
Palatal anomalies	51/165	31%
Asymmetric crying face	35/165	21%
Renal malformations	25/165	15%
Genital anomalies	19/165	11%

DIAGNOSIS OF DI GEORGE SYNDROME

Patients

The cohort was composed of 109 patients with clinical suspicion of 22q11.2 DS prospectively selected as part of a multicenter study, the Brazil's Craniofacial Project (CFBP). Before data collection, a standardized clinical protocol was established by all clinical geneticists, involved in this study. The protocol included physical examination, clinical and image investigation for palatal abnormalities (including data of nasopharyngoscopy), and cardiologic assessment (including echocardiogram). Also, included in the protocol was the collection of each patient's history of hypocalcemia and immunologic alterations/recurrent infections, growth and development, behavioral and neuropsychiatric disorders, and sensorineural and/or conductive hearing loss; as well as conducting neurologic, ophthalmologic, gastroenterologic, genitourinary, and skeletal evaluation.[7]

22q11.2 deletion syndrome is diagnosed in individuals with a submicroscopic deletion of chromosome 22 detected by fluorescence in situ hybridization (FISH), multiplex ligation-dependent probe amplification (MLPA), or chromosomal microarray (CMA). At present, fewer than 5% of individuals with clinical findings of the 22q11.2 deletion syndrome have normal routine cytogenetic studies and normal results on FISH testing; however, this figure may change as individuals with atypical or nested deletions within the DGCR (DiGeorge chromosome region) but not including the area encompassing the N25 or TUPLE FISH probes are identified using array-based or MLPA technologies.[8]

MANAGEMENT OF DIGEORGE SYNDROME

22q11DS is a multisystem syndrome with remarkable variability and expression among individuals. Moreover, the presence of one feature does not predict the presence of any other feature. As such, the management of 22q11DS patients is highly dependent on age and phenotype; therefore, treatment is individualized according to the underlying lesion and severity. [10,11]

In infants and young children with feeding problems, recurrent infections, hypocalcemia, and structural cardiac and palatal anomalies might be accompanied by speech, learning, and/or developmental difficulties. The combination of poor suck reflexes, palatal weakness, and dysfunctional swallowing often means that formula rests in abnormal anatomic locations or regurgitates into the Eustachian tube or sinuses. Gastroesophageal reflux is also common in these patients. The management of feeding difficulties includes thickeners, anti-reflux medications, and nasogastric or gastrostomic feeding tubes when necessary.[2,3,10,11]

Hypocalcemia due to hypoparathyroidism is a

common problem during the neonatal period, but it could occur at any age, including adulthood. The standard treatment for hypoparathyroidism is to correct hypocalcemia using oral vitamin D analogs and calcium. However, physicians should be careful to avoid overtreatment, which results in hypercalciuria, hypercalcemia, nephrolithiasis, nephrocalcinosis, and renal failure.[12] Teriparatide recombinant human parathyroid hormone (1–34) is a promising novel treatment for chronic hypocalcemia in hypoparathyroid syndromic children, and it might solve this problem in the future.[41] A recent study demonstrated the efficacy of parental parathyroid transplantation combined with allogeneic thymus transplantation in a patient.[6] Daily vitamin D is advised for 22q11DS patients of all ages with hypocalcemia; the dose should be the recommended daily allowance or as indicated therapeutically.[13]

Recurrent infections, particularly otitis media, might be an important problem during this period, and hearing loss might occur. Children should be treated appropriately for infections and followed carefully for potential hearing problems. Unrecognized hearing loss might contribute to delayed speech and cognitive development.[11,12,14,15]

Reconstituting the immune system is essential for patients with complete DGS, which can be accomplished by two methods: thymus tissue transplantation and a fully matched peripheral blood T-cell transplantation. Patients with complete DGS need to be protected from infections and blood products. Antifungal, antiviral, and antipneumocystis prophylaxis, and immunoglobulin replacement therapy should be commenced in these patients. Blood products could induce graft-versus-host disease when T-cells are absent. If necessary, patients should receive cytomegalovirus-negative and irradiated blood products. In addition, live viral vaccines should be avoided in patients with severe immunodeficiency.[13,16] Adverse events following live immunizations are typically minor and self-limited, suggesting that live vaccines could be considered in patients with mild-to-moderate immunosuppression.[16] As mentioned above, hypogammaglobulinemia might develop in patients with 22q11DS. For example, severe antibody deficiencies that are associated with lower respiratory tract infections and autoimmune conditions might occur. Therefore, patients should be screened for potential antibody deficiency.[14] Importantly, the degree of immunodeficiency cannot be predicted based on other phenotypic features and must be assessed individually in each patient with 22q11DS.[13]

Patients with 22q11DS have high death rates. Most deaths occur during the first year of life, and are associated with the presence of congenital heart diseases, particularly severe cardiac defects.[16] Right-sided heart failure, which is related to pulmonary vascular resistance, is a common complication of these anomalies, and was proposed to be an important contributor to mortality.[18] Surgical treatment is necessary for many of the cardiac problems in patients with 22q11DS. Nevertheless, individualized surgical approaches are needed according to the underlying cardiac lesion in each patient.[65] Laryngeal abnormalities are not rare and are important to recognize, particularly if cardiac surgery is planned. Therefore, complete ear, nose, and throat examinations and airway evaluations should be performed before any surgical procedure.[19]

As mentioned above, 22q11DS might affect many systems, and urinary ultrasonography should be performed after diagnosis. Children with 22q11DS should be screened for scoliosis, and surgical treatment might be necessary to correct this condition. Symmetric leg pain is seen frequently in 22q11DS patients during childhood, whereas asymmetric leg pain suggests other pathologies. Patients should also be screened for thyroid function and if necessary, thyroid morphology. Vomiting is common with 22q11DS, and can indicate a problem in the gastrointestinal system such as reflux or malrotation. If indicated clinically, patients should also be screened for autoimmune disorders such as Celiac disease. Subjects should also be screened for strabismus and refractive errors at 2 years or 3 years of age.[13,14]

The optimal management of patients with 22q11DS requires a comprehensive team approach, including specialists in genetics, pediatrics, endocrinology, plastic surgeons, immunologists, otolaryngologists, and speech therapists. 22q11DS is not a rare syndrome, and there is a need to form a local specialist team to ensure optimal management of affected patients. Appropriate guidelines for the management of patients are available in the literature, which contain useful information for physicians interested in 22q11DS syndrome.[13,14,20] 22q11DS might be difficult to recognize and diagnose in some patients, although the clinical findings for early diagnosis are known. Early diagnosis provides the best opportunity for modifying the course of the illness and optimizing patient outcome.

CONCLUSION

Symptoms of DiGeorge syndrome can be detected soon after the birth, especially that concerning congenital hearth disease. A prompt diagnosis and surgical intervention can save the child's life. Because of many other symptoms, many diagnostic procedures focused on this syndrome are to be performed, followed by long lasting stimulative treatment and treatment of seizures and psychiatric disorders.

Ethical Clearance- None

Source of Funding- Self

Conflict of Interest – Nil

REFERENCES

1. L. Lohmann, N. Chelloug, B. Rosales, C. Guérin, S. Lyonnet, P. Jonveaux and B. Simon-Bouy, Dicentric marker derived from chromosome 22 associated with mild clinical signs: a case report, Prenatal Diagnosis. (2000). 20, 2:156-158.
2. G.R. Jalali, J.A.S. Vorstman, Ab Errami, R. Vijzelaar, J. Biegel, T. Shaikh and B.S. Emanuel, Detailed analysis of 22q11.2 with a high density MLPA probe set, Human Mutation.2007. 29, 3:433-440.
3. De la Chapelle A, Herva R, Koivisto M, Aula 0. A deletion in chromosome 22 can cause DiGeorge syndrome. Hum Genet 1981;57: 253-256.
4. Mueller W, Peter HH, Wilken M, et al. The DiGeorge syndrome: clinical evaluation and course of partial and complete forms of the syndrome. Eur J Paediatr 1988;147:496-502.
5. L.J. Kobrynski, K.E. SullivanVelocardiofacial syndrome, DiGeorge syndrome: the chromosome 22q11.2 deletion syndromes. Lancet, 2007. 37: 1443-1452
6. MC Digilio, B Marino, R Capolino, and B Dallapiccola: Images Paediatr Cardiol. Apr-Jun 2005; 7(2): 23–34
7. Ilária C. Sgardioli, Társis P. Vieira, Milena Simioni, Fabíola P. Monteiro, and Vera L. Gil-da-Silva-Lopes J Pediatr Genetics. Mar2015; 4(1): 17–22.
8. Donna M McDonald-McGinn, MS, CGC, Beverly S Emanuel, PhD, and Elaine H Zackai, MD, FACMG. GeneReviews: February 28, 2013.
9. Digilio MC, Angioni A, De Santis M, Lombardo A, Giannotti A, Dallapiccola B, Marino B. Spectrum of clinical variability in familial deletion 22q11.2: from full manifestation to extremely mild clinical anomalies. Clin Genet. 2003;63:308–313
10. Bassett AS, McDonald-McGinn DM, Devriendt K, et al; International 22q11.2 Deletion Syndrome Consortium. Practical guidelines for managing patients with 22q11.2 deletion syndrome. J Pediatr. 2011;159(2):332–339
11. Habel A, Herriot R, Kumararatne D, et al. Towards a safety net for management of 22q11.2 deletion syndrome: guidelines for our times. Eur J Pediatr. 2014;173(6):757–765.
12 Horwitz MJ, Stewart AF. Hypoparathyroidism: is it time for replacement therapy? J Clin Endocrinol Metab. 2008;93(9):3307–3309.
13. Chinn IK, Markert ML. Induction of tolerance to parental parathyroid grafts using allogeneic thymus tissue in patients with DiGeorge anomaly. J Allergy Clin Immunol. 2011;127(6):1351–1355.
14. Maggadottir SM, Sullivan KE. The diverse clinical features of chromosome 22q11.2 deletion syndrome (DiGeorge syndrome). J Allergy Clin Immunol Pract. 2013;1(6):589–594.
15. Gennery AR. Immunological aspects of 22q11.2 deletion syndrome. Cell Mol Life Sci. 2012;69(1):17–27.
16. Hofstetter AM, Jakob K, Klein NP, et al. Live vaccine use and safety in DiGeorge syndrome. Pediatrics. 2014;133(4):946–954.
17. Repetto GM, Guzmán ML, Delgado I, et al. Case fatality rate and associated factors in patients with 22q11 microdeletion syndrome: a retrospective cohort study. BMJ Open. 2014;4(11):e005041.
18. Carotti A, Digilio MC, Piacentini G, Saffirio C, Di Donato RM, Marino B. Cardiac defects and results of cardiac surgery in 22q11.2 deletion syndrome. Dev Disabil Res Rev. 2008;14(1):35–42.
19. Leopold C, De Barros A, Cellier C, Drouin-Garraud V, Dehesdin D, Marie JP. Laryngeal abnormalities are frequent in the 22q11 deletion syndrome. Int J Pediatr Otorhinolaryngol. 2012;76(1):36–40.
20. Fung WL, Butcher NJ, Costain G, et al. Practical guidelines for managing adults with 22q11.2 deletion syndrome. Genet Med. epub 2015 Jan 8.