DYSPHAGIA AS AN EARLY PRESENTATION OF DIGEORGE'S SYNDROME – CASE REPORT

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Abstract

DiGeorge's syndrome is a 22q11.2 deletion leading to abnormal embryogenesis of pharyngeal arches and it is manifesting in a variety of clinical signs and symptoms. The spectrum of anomalies varies from minor facial dysmorphism and cleft palate to a broad spectrum of cardiovascular anomalies, thymic dysfunction and immune deficiencies, hypocalcemia due to hypoparathyroidism, growth and developmental delay and speech disturbances. Cardiovascular anomalies might include right sided aortic arch, aberrant vessels and vascular ring. Here we present an atypical case of partial DiGeorge's syndrome with feeding and swallowing difficulties and laryngeal stridor in the neonatal period. Early presentation in this period is usually due to severe hypocalcemia and cardiac disease. Feeding difficulties in a preterm baby needed clinical assessment skills in order to establish the diagnosis and delineate it from feeding difficulties usually seen in preterm babies. Esophagogram (barium X Ray) showed antero-posterior oblique impression towards the right side, the latero-lateral view showed impression on the rare side, suspected to be esophageal sub stenosis due to vascular anomaly, aberrant right subclavian artery and suspectedly hypoplasia. We report a 9-year follow up period of a subspecialist. The child had two surgeries due to aberrant vessel and velopharyngeal deficiency. Optimal management of patients with DiGeorge's syndrome requires a multidisciplinary teamwork which should include a cardiologist, immunologist, geneticist, speech/language therapist, endocrinologist and other subspecialists depending on patient's phenotype.

ДИСФАГИЈА КАКО РАНА ПРЕЗЕНТАЦИЈА НА DIGEORGE СИНДРОМ - ПРИКАЗ НА СЛУЧАЈ

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Извадок

DiGeorge Синдромот е резултат на делеција на 22q11.2 која води до промени во ембриогенезата на фарингалните органи. Симптомите кои се вклучуваат се сместени во пречениствена област. Кардиоваскуларните аномалии може да се вклучат во типа на десен артериален арцил, аберантни крвни суди и велофарингеален дефицит. Пациентите со синдром на DiGeorge треба да бидат следени од тим на субспецијалисти. Во тој период имаше две хируршки интервенции (корекција на аберантен артерија субклавија и суспектна хипоплазија на тимус). Пациентот беше следен во период од 9 години. Езофагограмот покажа коса импресија на антеро-постериорното правило со ориентација кон десно. Непцето но и со широк спектар на кардиоваскуларни аномалии, дисфункција на тимус и имун дефицитет, хипокалцемија поради хипопаратироидизам, пореметување во растот и развојот и проблеми во говорот. Кардиоваскуларните аномалии може да се од типот на десен артериален арцил, аберантни крвни суди и велофарингеален дефицит. Во овој приказ на случај пронизуваат атипичен случај на парадентален синдром на DiGeorge кој се презентираше со потешко во гоноштица и паранагализам страдер во неонатолниот период. Раната презентација на овој синдром во неонатолниот возраст нарасло се обиднува се во коса импресија на антеро-постериорното правило на езофагограмот како и во дисфагија. Пациентот беше следен од 9 години од тим на субспецијалисти.
Introduction

DiGeorge’s syndrome is a 22q11.2 deletion leading to abnormal embryogenesis of pharyngeal arches and it is manifesting in a variety of clinical signs and symptoms. The spectrum of anomalies varies from minor facial dysmorphism and cleft palate to a broad spectrum of cardiovascular anomalies, thymic disfunction and immune deficiencies, hypocalcemia due to hypoparathyroidism, growth and developmental delay and speech disturbances. Cardiovascular anomalies include right sided aortic arch, aberrant vesicles. When the aortic arc, or the associated vessels form a complete or incomplete ring around the trachea and the esophagus the condition is called vascular ring. It is rare congenital malformation that counts less than 1% of all heart anomalies. The symptoms are recognised usually during the period of early infancy or later in life, because of feeding and respiratory difficulties.

We present an atypical case of partial DiGeorge’s syndrome with feeding and swallowing difficulties and laryngeal stridor. Vascular ring should be suspected in all neonates with feeding and respiratory problems. Prompt diagnosis and treatment are of great importance for appropriate growth and development. In our case this condition is part of a syndrome, which should be carefully monitored by a multidisciplinary team.

Case report

One-month old infant was admitted to hospital due to feeding difficulties and vomiting. The condition was worsening during feeding. The baby was born premature, 33 weeks gestational age, birth weight 1860 gr, Apgar score 7/8. Polyhydramnios was noticed in the last trimester. She was treated in the nursery for 3 weeks and was tube fed. On admission, neonatal infection was suspected, although the baby had normal values of inflammatory markers. The plain chest X-ray showed displaced mediastinal organs towards the right side, the upper right lobe had lower transparency suspected as consolidation. The tracheal aspirate was positive for Klebsiella aerogenes and antibiotic treatment was started. The baby had intermittent laryngeal stridor and feeding difficulties. Fiberlaryngoscopy was normal. Esophagogram (barium X Ray) showed antero-posterior oblique impression towards the right side, the latero-lateral view showed impression on the rare side, suspected to be esophageal substenosis due to vascular anomaly, aberrant right subclavian artery. Thymic hypoplasia was also suspected. The baby had normal calcium and parathormone levels. Echocardiography showed patent ductus arteriosus. Computer tomography with contrast showed vascular ring with left sided aortic arch with aberrant right subclavian artery and patent ductus arteriosus. Renal ultrasound was normal. FISH (Fluorescence in situ hybridization) was performed showing 22 q11.2 micro deletion (Figure 1).

At the age of 4 months the child had an operation to correct the vascular anomaly. Afterwards she had regular cardiologic assessments, showing normal cardiac structure and function. Following the procedure, swallowing status improved. The
growth remained beneath the third percentile for 9 years follow up. Neurodevelopmental assessment showed developmental delay with delayed speech development, learning delays and disabilities. ERA was normal. At the age of 3 years the child was diagnosed Velopharyngeal deficiency (VPD) by a speech and language pathologist. She was referred to Cleft lip and palate craniofacial clinic where VPD confirmed via nasendoscopy. She was treated surgically with a posterior pharyngeal flap. She continued with speech therapy and was able to produce consonants for the first time and become intelligible to other people at the age of 5 years. Immunological assessment at age of 1 year showed normal function of the humoral immune system and neutrophil dysfunction. She was immunized by inactivated vaccines regularly. Cellular immunity could not be accurately assessed, and immunization with live vaccine (MRP) was not performed. During the 9 year follow up she had mild upper respiratory infections and two episodes of bronchopneumonia that required hospital treatment at her early age.

**Discussion**

DiGeorge’s syndrome features were first reported by Angelo DiGeorge in 1965 and 1968 although thymic aplasia was noted by Harrington in 1828 and the association with congenital hypoparathyroidism by Lobe in 1959. Additional anomalies were noted to be associated with the syndrome, especially anomalies of the great vessels, esophageal atresia, heart, ear, nose and mouth.
defects. For the first time the cause of the syndrome was suspected to be a deletion in chromosome 22q11 in 1981. This is a 35 mb chromosomal region that contains more than 35 genes that affect the morphogenesis of the pharyngeal arches, heart and brain.

DiGeorge's syndrome is one of the most common genetic disorders. It occurs in 1:4000 live births but could be higher having in mind the clinical variability. More than 180 different defects have been associated with the syndrome. Typical presentation during infancy usually includes some of the following features: facial dysmorphia, heart defect, hypocalcemia, palatal anomalies and immunodeficiency. The standard method for diagnosis of DiGeorge’s syndrome is the specific FISH test for chromosome 22q11 deletions. Due to the wide availability of these specific probes, clinicians can diagnose affected children, often presenting with cardiac abnormalities, immunodeficiency or hypocalcemic seizures.

This syndrome is rarely diagnosed in the neonatal period. Early presentation in this period is usually due to severe hypocalcemia and cardiac disease.

We present a rare case of early diagnosed patient in the neonatal period with feeding difficulties and swallowing problems. Our patient was a preterm baby, 33 weeks of gestation that stayed in the nursery for 3 weeks and was tube fed. She started having feeding difficulties when she was discharged home and was bottle fed. Feeding difficulties in a preterm baby needed clinical assessment skills in order to establish the diagnosis and delineate it from feeding difficulties usually seen in preterm babies. The patient was admitted to our Clinic with aspiration-based infection as it has been previously reported.

Feeding difficulty is often a symptom of palatal dysfunction, cardiac anomalies and gastrointestinal dysmotility, as a result of the presence of a vascular ring that impairs the esophagus, and hypotonia can lead to feeding difficulty. In some patients, these difficulties likely result from craniofacial dysmorphology including cleft palate and other anomalies that often require surgical intervention. Dysphagia can be seen in different developmental disorders including DiGeorge's syndrome. As a symptom it may be present during infancy and may last with complications until the age of 4 years and sometimes onwards.

In our case, barium esophagogram showed esophageal sub stenosis due to vascular anomaly, aberrant right subclavian artery. And thymic hypoplasia or agenesis was suspected. The first report of symptomatic aberrant right subclavian artery was published in 1735, and in 1794 the term dysphagia lusoria was used to describe ARSA that has a retroesophageal course.

Association of left sided aortic arch with aberrant right sided aortic arch and ipsilateral patent ductus arteriosus in a patient with DiGeorge's syndrome as seen in our patient was only described by Taliana et al.

Conclusion

We present a rare case of DiGeorge's syndrome in a preterm infant with dysphagia due to aberrant right
subclavian artery. This was a case with a challenging diagnosis, in which classical manifestations of DiGeorge’s syndrome was initially lacking. We report a 9-year follow up period by a team of subspecialists. The child had two surgeries due to aberrant vessel and velopharyngeal deficiency. Optimal management of patients with DiGeorge’s syndrome requires a multidisciplinary team. The team should include a cardiologist, immunologist, geneticist, speech/language therapist, endocrinologist and other subspecialists depending on patient’s phenotype, as reported in our case.

References
1. A comment on another paper, Cooper M., Peterson R., Good R. A new concept of the cellular basis of immunity. The Journal of Pediatrics.1965;67(5):907.
2. DiGeorge AM. Congenital absence of the thymus and its immunologic consequences: concurrence with congenital hypoparathyroidism. IV(1). White Plains, NY: March of Dimes-Birth Defects Foundation. 1968;116-21.
3. Harrington LH. Absence of the thymus gland. Lond Med Gaz 1929;3:314.
4. Lobdell DH. Congenital absence of the parathyroid glands. Arch Pathol 1959;67:412-18.
5. Lischner HW. DiGeorge syndrome(s). Pediatr 1972;81: 1042-4.
6. De la Chapelle A, Herva R, Koivisto M, Aula O. A deletion in chromosome 22 can cause DiGeorge syndrome. Hum Genet 1981;57:253-256.
7. Kobrynski LJ, Sullivan KE.
8. Velocardiofacial syndrome, DiGeorge syndrome: the chromosome 22q11.2 deletion syndromes. Lancet 2007;370(9596):1445–1452.
8. 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.
9. Emanuel BS. Molecular mechanisms and diagnosis of chromosome 22q11.2 rearrangements. Dev Disabil Res Rev 2008;14(1):11–18.
10. Hurles M. How homologous recombination generates a mutable genome. Hum Genomics 2005;2(3):179–186.
11. Shprintzen RJ. Velo-cardio-facial syndrome. In: Cassidy SB, Allanson JE, editors. Management of genetic syndromes, 2nd ed. Hoboken: Wiley-Liss, 2005:615– 631.
12. McDonald-McGinn DM, Kirschner R, Goldmuntz E, Sullivan K, Eicher P, Gerdes M, et al. The Philadelphia story: the 22q11.2 deletion: report on 250 patients. Genet Couns 1999;10:11-24.
13. Yakut T, Kilic SS, Cil E, Yapici E, Egeli U. Pediatr Surg Int 2006; 22(4):380-3
14. Dogus Vuralli. Clinical approach to hypocalcemia in newborn period and infancy: Who should be treated? International Journal of Pediatrics 2019, Article ID 4318075
15. Hopkin RJ, Schorry EK, Bofinger M, Saal HM. Increased need for medical interventions in infants with velocardiofacial (deletion 22q11) syndrome. J Pediatr 2000; 137: 247–249.
16. Trinick R, Johnston N, Dalzell AM,
McNamara P S. Reflux aspiration in children with neurodisability – a significant problem, but can we measure it? J Pediatr Surg 2012; 47, 291–298.

17. Oskarsdóttir S, Vujic M, Fasth A. Incidence and prevalence of the 22q11 deletion syndrome: a population-based study in Western Sweden. Arch Dis Child 2004;89:148–151.

18. Botto LD, May K, Fernhoff PM, et al. A population-based study of the 22q11.2 deletion: phenotype, incidence, and contribution to major birth defects in the population. Pediatrics 2003;112:101–107.

19. Eicher P S. et al. Dysphagia in children with a 22q11.2 deletion: unusual pattern found on modified barium swallow. J Pediatr 2000; 137 (2):158-164.

20. Williams GD, Schmeckebier M, Edmonds H W, Grand E G. Variations in the arrangement of the branches arising from the aortic arch in the American whites and negroes. The Anatomical Record 1932; 54: 247–251.

21. Bayford D. An account of a singular case of obstructed deglutition. Memoirs of the Medical Society of London1794; 2: 275–286.

22. Taliana N, Gatt A, Borg A, Grech V. The rarest aortic arch anomaly: a case report of asymptomatic isolation of the subclavian artery. Images Paediatr Cardiol 2017;19(2):9-12.