OPEN ACCESS Freely available online

Clinical Pediatrics: Open Access

Review

Clinical Utility of Genetic Screening for 22q11.2 Deletion in a Cleft Palate Population and Interest of the Microarray Analysis

Oumama El Ezzi*, Christelle Jung and Anthony S de Buys Roessingh

Department of Pediatric Surgery, SCEA, University Hospital Center of the Canton of Vaud (CHUV), Switzerland

ABSTRACT

Aim: 22q11.2 deletion syndrome is one of the most common syndromes. Its prevalence among children with isolated cleft palate is estimated to be one in 100. The purpose of this study is to evaluate whether routine screening for 22q11 deletions in all infants with cleft palate (CP) is a good strategy for early detection.

Methods: This prospective study was conducted from January 2014 to December 2017 in our cleft lip and palate multidisciplinary consultation at the University Hospital of Lausanne (CHUV). Genetic screening using the Fluorescence In Situ Hybridization (FISH) method has been routinely used to all new patients with CP to identify the chromosome 22q11.2 deletion syndrome.

Results: During the study period, 30 children with CP were treated in our Cleft Center. None of these patients had the 22q11.2 deletion syndrome.

Conclusion: In our opinion, there is no significant advantage in organizing a systematic screening of our children with isolated CP. These patients should be followed closely to enable the detection of other clinical features that could lead to a 22q11DS diagnosis. Extensive information on 22q11DS should be widely furnished.

Keywords: Cleft palate; Deletion 22q11; Screening; Velopharyngeal insufficiency; Genetics

INTRODUCTION

The chromosome 22q11.2 deletion syndrome (22q11DS) is one of the most common genetic syndromes. It shows an autosomal dominant inheritance pattern [1] and is inherited in 10% of cases. It is due to the microdeletion of the long arm of chromosome 22 at the q11.2 band, and can be detected by the Fluorescence In Situ Hybridization (FISH) method [2]. It is present in approximately one in 4000 live births [3]. Its diagnosis is based on a number of diverse, more or less severe symptoms, and can then be confirmed by genetic testing by the FISH method or, more frequently; by chromosomal microarray that has the advantage of giving information about all chromosomes. These symptoms include congenital cardiovascular malformation, dysmorphic facial appearance, recurrent infections, increased risk of autoimmune disease, developmental delay, possible long-term schizophrenia, and palatal anomalies such as cleft palate (CP) and velopharyngeal insufficiency (VPI) [4]. Other anomalies may occur with variable frequency.

This deletion may strongly affect the child development and its early detection and management may help to reduce its impact.

In our capacity as cleft surgeons, in contact with patients from birth or even antenatally, we do recognize that an early detection of the deletion in children born with a CP would allow appropriate counselling and early management of the syndrome. We nevertheless try to evaluate, in this study, the usefulness of routine testing for the microdeletion of 22 q11DS in children born with cleft palate during the palatal cleft repair.

We then propose our data associated to a review of the available studies about the utility of genetic screening for 22q11DS deletion in children born with cleft palate.

MATERIALS AND METHODS

We conducted a monocentric prospective study including all children referred to our cleft lip and palate multidisciplinary consultation at the University Hospital of Lausanne (CHUV)

***Correspondence to**: Oumama El Ezzi, Department of Pediatric Surgery, SCEA, University Hospital Center of the Canton of Vaud (CHUV), CH-1011 Lausanne, Switzerland, Tel: +41795561604; E-mail: oumama.el-ezzi@chuv.ch

Received: October 14, 2019; **Accepted**: January 14, 2020; **Published**: January 21, 2020

Citation: El Ezzi O, Jung C, De Buys R, AS (2020) Clinical Utility of Genetic Screening for 22q11.2 Deletion in a Cleft Palate Population and Interest of the Microarray Analysis. Clin Pediatr OA 5:181. doi: 10.35248/2572-0775.20.5.161

with a pre- or post-natally diagnosed CP and then tested for the 22 q11.2 deletion. Informed consents to the testing were signed by the parents after they had been given detailed information to about the 22q11DS and its implications in the future. In accordance with the protocol, a FISH blood test for 22q11 was performed at the time of the CP repair on children aged from four to six months. The blood sample was obtained at the beginning of the general anesthesia. It was not painful, and did not perturb the progress of the anesthesia or prolong the duration of surgery. The cost of the screening was covered by the insurance companies. The analysis was performed on cultured cells using Cytocell® probe in the laboratory of constitutional cytogenetics of our institution.

At the time of the test, none of these patients had undergone any previous screening. Other forms of facial clefts, such as unilateral or bilateral complete clefts or isolated lip clefts, were excluded from this study.

RESULTS

Thirty children, 19 females and 11 males, born with a CP from January 2013 to December 2017 and treated in our pediatric surgery department were included in this study. There were 20 cases of total cleft palate, nine of soft palate cleft, and one of sub-mucous cleft. Associated anomalies were found in nine patients: Pierre Robin Sequence [5] in five patients, Pterygium Coli syndrome [6] in one patient, Treacher Collins syndrome [7] in one patient and structural brain abnormalities diagnosed on radiologic imaging in two patients (Table 1). All the patients in our series underwent the FISH test for 22q11DS. We did not find this chromosomal deletion in this prospective screening, but other chromosomal abnormalities were found in two patients: One had a chromosome four deletions associated with the duplication of chromosome eight, and the other a non-specific deletion without clinical manifestation.

Patients	Number
Isolated CP	11
Pierre Robin Sequence	5
Pterygium Coli Syndrome	1
Treacher Collins Syndrome	1
Brain abnormalities	2

Table 1: Patient distribution

For comparison, of the 17 confirmed cases of 22q11DS followed in a dedicated multidisciplinary consultation in the general pediatric department of our hospital, two patients (11.7%) had a total CP and one (5.8%) a sub-mucous cleft and ten had VPI (29.4%).

DISCUSSION

22q11DS is one of the most frequently encountered microdeletion syndromes, concerning about one in 4000 births and affecting males and females equally [8]. Its clinical manifestations have been widely documented, and although they do vary considerably from child to child, they nevertheless present numerous common clinical features. The presence and severity of the phenotypic expression of the syndrome varies from child to child, as also does the initial onset of symptoms and their development. With a broad phenotypic spectrum, it seems important to recognize the different clinical manifestations to be able to make the diagnosis as early as possible.

Neonatal hypocalcemia caused by hypoparathyroidism is considered one of the cardinal symptoms of the syndrome, but it may be mild or transient, and missed in some patients [9-11]. Conotruncal and aortic arch defects are the most typical cardiac malformations associated with the syndrome and the main cause of early mortality [12]. Typical facial characteristics associating asymmetric crying facies, hypertelorism, hooded eyelids, tubular nose, small mouth, and mild ear abnormalities are considered the main presenting features [13]. Thymic abnormalities including agenesis or hypoplasia, T-cell deficiency, atypical infections, severe immunodeficiency, diminished antigenic response and humoral immunity are common signs of a 22q11DS [14].

Behavioral, cognitive and psychiatric disorders that can be severe are more frequent in cases of 22q11DS than in the general population and lead to widely variable phenotypes [15]. Schizophrenia is the most frequent abnormality associated with the 22q11DS, present in 60% of patients with the syndrome. But other psychiatric disorders include attention-deficit/hyperactivity disorder (ADHD), anxiety and affective disorders, autism spectrum disorders (ASD) and psychotic disorders. Half of these patients have some level of cognitive impairment. Behavioral differences include impulsivity, emotional lability, shyness and disinhibition [16-18].

The phenotype of palatal anomalies and velopharyngeal dysfunction is also highly variable. Cleft palate has been reported in 11% of syndromic patients, sub-mucous cleft palate in 16%, and VPI in 27% [19]. Our series has the same proportions as those reported in the literature.

In general, congenital cardiac defects associated with neonatal hypocalcemia are the most frequent features that lead to the diagnosis in the first months of life [20]. Associated conditions may involve multiple other organs systems and cause, among others, kidney problems, hearing loss, ophthalmological/dental alterations and skeletal malformations [21].

Malformations or syndromes associated with oro-facial clefts are more frequent in children with CP. Isolated CP occurs in one in 1,500 live births and may be associated with more than 400 genetic and syndromic disorders [22,23]. The 22q11DS is found in 9 to 11% of patients with isolated CP [24]. The benefit of a routine screening for 22q11 deletions has been largely debated in the literature. Based on a series of 58 patients, Ruiter et al. concluded that the prevalence of 22q11 deletions among patients with isolated overt CP is rather low (1%), and that it is therefore not necessary to screen all patients with CP [25]. Later, in 2008, Bashir et al. ran the 22q11 FISH test on 134 patients

with different kind of oro-facial cleft, and obtained a positive result in nine (6.7%) of these patients, which is not negligible. This led them to conclude that routine widespread screening is not only indicated, but necessary for the early management of velopharyngeal insufficiency, endocarditis prophylaxis, prevention of infection in the context of immunodeficiency, and the positive impact of an early intervention on reading, language and mathematical abilities, motivation and self-esteem [26]. More recently, a systematic review of 328 patients published in 2016 revealed that the prevalence of 22q11DS in children with isolated CP was relatively low 0.3%. Routine screening was therefore not recommended for patients with isolated CP [27].

Our study on a small population suggests that the mere presence of CP in a newborn child does not justify systematic testing for 22q11DS in all patients. We therefore also feel that there is no significant advantage in organizing a systematic screening of our children with isolated CP. These patients are closely followed in our cleft lip and palate multidisciplinary consultation until they are fully grown, and particular attention is paid to the detection of other clinical features that could lead to a 22q11DS diagnosis. We feel that the very low incidence of this chromosomal abnormality among children with isolated CP does not justify an additional stress for parents who already have to deal with the cleft malformation.

It is obvious that the sample size of the present single center study is limited and does not allow any conclusions to be drawn about the usefulness of the screen. A much larger sample or a multicentric study is needed.

Finally, chromosomal microarray would have been more appropriate for patients with CP and associated malformations presented in our series.

CONCLUSION

Based on our review of the literature and on our own experience, we suggest that the routine screening for 22q11DS of children born with isolated CP is not to be recommended. The screening is fully justified in children who present other clinical signs and symptoms that could be associated with the syndrome. These symptoms must be discussed in multidisciplinary meetings in order to detect this possible deletion as early as possible, and to guarantee an optimal management of these children during their early growth and development. Extensive information on 22q11DS should be furnished to caregivers to promote early diagnosis and global support.

ACKNOWLEDGEMENTS

The authors are grateful to Annette Wagnière for reviewing the English text and to the laboratory of constitutional cytogenetics for technical support.

REFERENCES

1. Scambler PJ. The 22q11 deletion syndromes. Hum Mol Genet. 2000;9(16),2421-2426.
2. Brunet A, Gabau E, Perich RM, Valdesoiro L, Brun C, Caballín MR, et al. Microdeletion and microduplication 22q11.2 screening in 295 patients with clinical features of DiGeorge/Velocardiofacial syndrome. Am J Med Genet Part A. 2006;140A(22):2426-2432.
3. Botto LD, May K, Fernhoff PM, Correa A, Coleman K, Rasmussen SA, 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(1 Pt 1):101-107.
4. Shprintzen RJ. Velo-cardio-facial syndrome: 30 years of study. Dev Disabil Res Rev. 2008;14(1):3-10.
5. Giudice A, Barone S, Belhous K, Morice A, Soupre V, Bennardo F, et al. Pierre Robin sequence: A comprehensive narrative review of the literature over time. J Stomatol Oral Maxillofac Surg. 2018;119(5):419-428.
6. Gorlin R J, Sedano HO, Cervenka, J. Popliteal pterygium syndrome. A syndrome comprising cleft lip-palate, popliteal and intercrural pterygia, digital and genital anomalies. Pediatrics. 1968;41(2):503-509.
7. Trainor PA, Dixon J, Dixon MJ. Treacher Collins syndrome: Etiology, pathogenesis and prevention. Eur J Hum Genet. 2009;17(3):275-283.
8. Oskarsdottir 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(2):148-151.
9. Stagi S, Lapi E, Gambineri E, Manoni C, Genuardi M, Colarusso G, et al. Bone density and metabolism in subjects with microdeletion of chromosome 22q11 (del22q11). Eur J Endocrinol. 2010;163(2):329-337.
10. Brauner R, Le Harivel de Gonneville A, Kindermans C, Le Bidois J, Prieur M, Lyonnet S, et al. Parathyroid function and growth in 22q11.2 deletion syndrome. J Pediatr. 2003;142(5):504-508.
11. Al-Jenaidi F, Makitie O, Grunebaum E, Sochett E. Parathyroid gland dysfunction in 22q11.2 deletion syndrome. Horm Res. 2007;67(3):117-122.
12. Momma K. Cardiovascular anomalies associated with chromosome 22q11.2 deletion syndrome. Am J Cardiol. 2010;105(11):1617-1624.
13. Oskarsdottir S, Holmberg E, Fasth A, Stromland K. Facial features in children with the 22q11 deletion syndrome. Acta Paediatr 2008;97(8):1113-1117.
14. Finocchi A, Di Cesare S, Romiti ML, Capponi C, Rossi P, Carsetti R, et al. Humoral immune responses and CD27 + B cells in children with DiGeorge syndrome (22q11.2 deletion syndrome). Pediatr Allergy Immunol. 2006;17(5):382-388.
15. Murphy KC. Schizophrenia and velo-cardio-facial syndrome. Lancet. 2002;359:426-430.
16. Bertran M, Tagle FP, Irarrazaval M. Psychiatric manifestations of 22q11.2 deletion syndrome: A review of the literature. Neurologia. 2018;33(2):121-128.
17. Tang KL, Antshel KM, Fremont WP, Kates WR. Behavioral and psychiatric phenotypes in 22q11.2 deletion syndrome. J Dev Behav Pediatr. 2015;36(8):639-650.
18. Norkett EM, Lincoln SH, Gonzalez-Heydrich J, D'Angelo EJ. Social cognitive impairment in 22q11 deletion syndrome: A review. Psychiatry Res. 2017;253(1):99-106.
19. Metcalfe K. Cardiac problems in genetic syndromes. Paediatrics and Child Health. 2018;28(12):574-578.
20. Oskarsdottir S, Persson C, Eriksson BO, Fasth A. Presenting phenotype in 100 children with the 22q11 deletion syndrome. Eur J Pediatr. 2005;164(3):146-153.
21. McDonald-McGinn DM, Sullivan KE. Chromosome 22q11.2 deletion syndrome (DiGeorge. syndrome/velocardiofacial syndrome). Medicine (Baltimore). 2011;90(1):1-18.
22. Mossey P. Epidemiology underpinning research in the aetiology of orofacial clefts. Orthod Craniofac Res. 2007;10(3):114-120.

23. Mossey PA, Little J, Munger RG, Dixon MJ, Shaw WC. Cleft lip and palate. Lancet. 2009;374(9703):1773-1785.

24. 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.

25. Ruiter EM, Bongers EMHF, Smeets DFCM, Kuijpers-Jagtman AM, Hamel BCJ. No justification of routine screening for 22q11 deletions in patients with overt cleft palate. Clin Genet. 2003;64(3):216-219.

26. Bashir M A, Hodgkinson P D, Montgomery T, Splitt M. 22q11 deletion in children with cleft lip and palate e is routine screening justified? J Plast Reconstr Aesthet Surg. 2008;61(2):30-132.

27. Panamonta V, Wichajarn K, Wongswadiwat Y, Panamonta M, Pradubwong S, Chowchuen B. Assessment of Chromosome 22q11.2 deletion in patients with isolated cleft palate: A systematic review of prospective studies. J Med Assoc Thai. 2016;99(Suppl 5:):S194-S198.