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 22q11DS 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).
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.

Table 1: Patient distribution

<table>
<thead>
<tr>
<th>Patients</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated CP</td>
<td>11</td>
</tr>
<tr>
<td>Pierre Robin Sequence</td>
<td>5</td>
</tr>
<tr>
<td>Pterygium Coli Syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Treacher Collins Syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Brain abnormalities</td>
<td>2</td>
</tr>
</tbody>
</table>

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 38 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.
REFERENCES


