Case Report

Description of a child with a 6q14.1–q16.1 interstitial deletion: A very rare entity with airway manifestations

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1. Introduction

Deletions of the long arm of chromosome 6 were first described in 1973 by Mikkelsen et al. and they constitute rare genetic anomalies that usually occur \textit{de novo} [1]. There are less than a hundred cases described worldwide and the phenotypes vary according to the size and location of the deleted region, although some common characteristics are found, such as developmental delay, hypotonia, facial dysmorphisms, micrognathia, microcephaly, ear anomalies, inguinal and/or umbilical hernias and cardiac malformations [2–4]. Hopkin and its colleagues proposed the existence of three phenotypic groups, according to the deleted region. The first group would include the proximal deletions (6q11–q16), frequently associated to hernias, upslanting palpebral fissures and thin lips; the second one would include the medial deletions (6q15–q25), associated to an intrauterine growth retardation, respiratory distress, hypertelorism and upper limb malformations; finally, the third group would concern the terminal deletions (6q25–qter), associated to retinal abnormalities, cleft palate and genital hypoplasia [2]. A search of the published literature allowed the gathering of more specific and diagnostic features related to the first group (6q11–q16). We point out the presence of epicanthus, large nasal tip, anteverted nares, wide philtrum, asymmetric face, large ears, short neck and excess cervical skin folds. Joint hypermobility and instability are also present [5,6].

The authors observed that there is less information available from bibliographic sources when searching for more specific microdeletions. Valtat et al. described two 6q14–q16 interstitial deletions present in patients with motor and mental retardation and facial dysmorphic features. One of them had congenital stridor [7]. More recently, Wentzel et al. studied two patients with \textit{de novo} deletions in the 6q14–q15 region, whose most characteristic aspects, beyond a developmental delay, were obesity, round face and thick superior eyelids [8]. A couple of other patients with overlapping 6q14 deletions were described by Becker et al., presenting developmental delay and characteristic dysmorphic features [9].

In this paper, the authors describe the case of a female infant with a 6q14.1–q16.1 interstitial \textit{de novo} deletion, with 12.71 Mb size. Besides several dysmorphic features, this patient also presented laryngotraceobronchomalacia, seromucous otitis and gastro oesophageal reflux.

2. Case report

This female infant is the youngest daughter of a healthy and unrelated couple, a 29 year-old mother and a 32 year-old father. The pregnancy was described as uneventful and she was born vaginally at the 40th week gestation, with no complications. She
displayed normal Apgar scores (9/10), 3090 g of weight, 50 cm of length and 34 cm of head circumference. Routine biochemical and metabolic screenings were normal. The newborn was referred to otorhinolaryngology at 4 weeks of age, due to stridor and noisy breathing present since the neonatal period, especially when being fed and when agitated. She was also referred due to a failure in the hearing screening tests – otoacoustic emissions (OAEs) and automated auditory brainstem response (ABR). There were no episodes of cyanosis, facial congestion, cough or gasping described. On examination, she presented a good vitality with a noisy breathing and a reduction of the air flow through the right nostril, raising the suspicion of a partial choanal atresia. Therefore, she underwent a sinus computed tomography (CT) scan that excluded a choanal atresia and showed a minor nasal septum right deviation.

At 7 weeks of age the proband was observed by a geneticist that described a well-proportioned and symmetric baby, with an axial hypotonia, a big anterior fontanelle extending through the metopic suture, horizontal nystagmus, converging strabismus, small and upsloping palpebral fissures, wide and planed philtrum, excess infraorbital skin folds, downsloping mouth corners, thin upper lip with a cupid’s arch shape, retrogotatism, low set and posteriorly rotated auricles with a wrapped helix (Figs. 1 and 2), umbilical hernia, anterior anus, sacral dimple with a bilateral sinus opening and 5 café au lau spots. An array comparative genomic hybridization (CGH) was performed and an interstitial deletion with clinical significance was detected. It corresponded to the 6q14.1–q16.1–arr[hg19] 6q14.1q16.1(81,728,627–94,438,332) × 1 region. The size of the deletion was 12.71 Mb and it contains about 36 Online Mendelian Inheritance in Man (OMIM) genes, for a total of 95 genes in this region, according to the reference genome hg19 (Fig. 3). The analysis was performed using the high resolution platform CGX-HD 180K (Signature Genomics, PerkinElmer) and the data were analyzed with the Genoglyphix™ v3.0 software. The parent’s karyotype analysis excluded a chromosomal rearrangement, so the conclusion was that it was a de novo anomaly.

Although the stridor persisted, the laryngotracheobronchoscopy was delayed until the child was one year old due to several respiratory infections, most of them bronquiolitis and some of them requiring hospital surveillance, due to aggravation of stridor. The endoscopy was then performed under general anesthesia and revealed a long and tubular epiglottis and an excess of aritnoid mucosa, collapsing to the glottis during the inspiration. The aryepiglottic folds were not shortened. Tracheobronchomalacia was also present, more severe at the left bronchi, with no other lesions associated (Figs. 4–7). The patient was kept under surveillance in several medical areas and performed other complementary exams to investigate the presence of additional anomalies. The brain magnetic resonance (MRI), the spine X-ray, the cardiac, abdominal and renal egeography were all normal. The hearing tests repeated at 4 months of age were also normal and the
them are overlapping deletions. Besides several dysmorphic features, the patient had also laryngotracheobronchomalacia with no signs of clinical severity, but requiring surveillance, seromucous otitis during the first months of life and gastro oesophageal reflux managed with conservative measures [10].

The presented genetic disorder can be included in the first Hopkin et al. group described above. The clinical features are in consonance to this wider group but also with many of the phenotypic characteristics already known for the 6q11–6q16 interval, published in 2011 by the Unique–Rare Chromosome Disorder Support Group. In this publication there is a small number of children with airway difficulties due to laryngotracheobronchomalacia, 3 of them requiring tracheostomy. There are also descriptions of seromucous otitis and gastro oesophageal reflux [5].

After an extensive bibliographic revision we can confirm that there are very few comparable microdeletions. Both 6q14–q16 deletions described by Valtat et al. were detected by conventional cytogenetics and presented a global developmental delay and facial dysmorphisms–bilateral epicanthus, thin upper lip and wide nasal tip. One of them also presented upslanting palpebral fissures, similar to our patient. The other one had a congenital stridor, anteverted nostrils, low set ears, a high palate and a short neck [7]. Grati et al. [11] reported another similar case that was detected during pregnancy in a fetus with minor facial dysmorfisms and limb contracture. More recently, a study by Wentzel et al. described 2 patients with de novo defects in the 6q14–q15 region. The most characteristic aspects, besides the developmental delay, were early onset obesity, round face and thick superior eyelids. These authors also reported another microdeletion characterized by important and comparable features like stridor and noisy breathing due to esophagus’ tracheal compression, a global developmental delay, hypotonia, oesophageal reflux, feeding difficulties requiring gastrostomy, sacral dimple, wide nose and philtrum, large ears, seromucous otitis, nystagmus and short neck [8,12].

In the analysis and description of 2 patients with overlapping 6q14 deletions, Becker et al. suggested the existence of a contiguous genetic syndrome that would exhibit variable phenotypes according to the size and location of the defect [9].

A lot of the features described above are comparable to the ones presented by our patient, especially some of the facial dysmorphisms and the global cognitive and neuromotor developmental delay, of which the laryngotracheobronchomalacia might be a manifestation. Although this is the most common laryngeal disease of infancy, often associated with congenital or acquired neuromuscular disorders, it is not described in the published 6q14–6q16 deletions. It is only described in the already mentioned Unique–Rare Chromosome Disorder Support Group publications, which include the wider interval 6q11–6q16 [5,13].

One of the genes proposed as responsible for some of the aspects described is the Ephrin 7 receptor (EphA7), which is in the 6q16.1 region and is part of the Eph/ephrin family of tyrosin kinases receptors (RTK). This gene has been demonstrating some relevance in the central nervous system development during the embryogenesis and its absence might be responsible for the cognitive and motor defects, shared by all patients [4,14,15]. Other possible candidates for anomalies in the deleted area are FILIP1, MYO8B, HTR1B and SNX14, in the 6q14 region [9].

In conclusion, the limited number of available cases and the great variability of genetic defects that can arise, make the information about each specific microdeletion very limited and so the genotype–phenotype correlation is difficult. Nevertheless, with this case, the authors aim to contribute with additional information so that we can continue delineating genes associated to particular phenotypes.

### 3. Discussion

The presented case displays a 6q14.1–q16.1 deletion with 12.71 Mb size identified by array CGH, which allowed the definition of the breaking points and their dimension with a greater precision. According to the DECIPHER database, this specific microdeletion is registered in 78 patients and some of tympanogram that was showing a type B curve up until then, normalized afterwards. This type B curve was probably due to a seromucous otitis and was interpreted as a possible cause for the failure in the initial hearing tests.

In our last observation at 24 months, the patient showed a developmental delay, a reduction in the stridor and complaints of gastro oesophageal reflux.
Conflict of interest

The authors declare that they have no conflict of interest.

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References
