ORIGINAL STUDY

Noses in dysmorphology - do we know all about the nose?

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ABSTRACT

OBJECTIVE. To describe different abnormalities that can be found in the structure of the nose as encountered in various genetic conditions.
MATERIAL AND METHODS. Retrospective chart study collecting the medical data regarding the aspect of the nose in different genetic syndromes diagnosed in patients admitted in the Paediatric Neurology Department of the "Alexandru Obregia" Clinical Psychiatric Hospital in Bucharest.
RESULTS. The dysmorphology of the nose is extremely complex, related to different genetic mutations. There are variations in length, width, shape involving the nasal bridge, the nasal tip, the columella or choanal atresia, which can be found isolated or associated in different genetic syndromes.
CONCLUSION. There are many variations in the aspect of the nose as related to different gene mutations. The nasal phenotype can be used to diagnose different genetic diseases.
KEYWORDS: nose dysmorphology, genetic mutations

INTRODUCTION

The nose is one of the most described parts of the body, both in art and medicine. Probably the most famous description of a nose in history is that of the french philosopher Blaise Pascal, in his *Pensées*, of the Egyptian queen Cleopatra: "Cleopatra's nose, had it been shorter, the whole face of the world would have been changed."

The nose has different aspects regarding shape, size, features and general appearance from one person to another. There are very different appearances of the nose in the normal population. When the nasal structures present a conformation not found within the normal variation, we can think that this could be related to a genetic syndrome, especially if they are associated with other symptoms[1]. A proper description of the nose is very important in dysmorphology, the discipline which puts together all particular features of an individual in order to identify a genetic syndrome.

From all 5492 syndromes listed in the London Dysmorphology Database, 1316 syndromes present nose symptom(s), including alterations of the nasal bridge (841 syndromes), the nasal tip (254 syndromes), the nasal alae (132 syndromes), the nares (314 syndromes), the nasal septum (39 syndromes), the columella (52 syndromes) and abnormal smell (30 syndromes)[1].

MATERIAL AND METHODS

As a method of research, we used a retrospective chart study. We collected the medical data recorded in the hospital charts of the patients admitted in the Paediatric Neurology Department of the "Alexandru Obregia" Clinical Psychiatric Hospital in Bucharest, during a 5-year period, between January 1st 2007 and December 31st 2012. The data regarding the aspect of the nose were correlated with the whole phenotypic aspect of the patient. Different genetic syndromes were diagnosed in the study group.

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The diagnostic was sustained by genetic testing (more than 90% of our patients underwent this testing), various genetic abnormalities being diagnosed in the patients included in the study. Many genetic syndromes include modifications of the shape, size or other features of the nose.

The study inclusion criteria were the abnormality of the nose as noticed during the clinical examination of paediatric patients. The exclusion criteria was represented by patients with nasal trauma.

Clinical photos were used to certify the existence of the alterations we found.

RESULTS

1. Variations in Length and Width

1.1. Long nose

Length is the distance from nasion to subnasion. A nose is defined as long if it measures more than two standard deviations (SD) above the mean or there is an apparently increased length from the nasal root to the nasal base[3].

Among our patients, we identified a girl with Rubinstein-Taybi syndrome, a genetic condition characterized by short stature, distinctive facial features, long nose (Figure 1), moderate or severe intellectual disability, broad thumbs and first toes. The determining factor is represented by a defect in a gene that leads to abnormal protein substances called EP300 and CREBBP.

Figure 1 Long nose in a patient with Rubinstein-Taybi syndrome

1.2. Prominent Nose

A nose is defined as prominent if there is an increased distance between subnasale and pronasale (nasal protrusion) (Figure 2)[3].

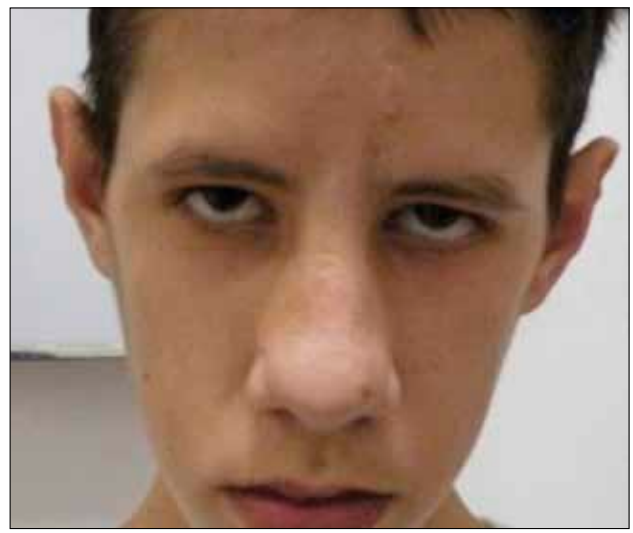

Figure 2 Prominent nose

2. Choanal atresia

Choanal atresia is defined as a blocked back of the rhino-pharyngeal passage (choana)[4]. It is an important feature of CHARGE syndrome, in association with coloboma, heart defects, retardation of the growth and/or development, genital defect and ear anomalies and/or deafness (Figure 3). The mutations of the gene *CHD7* were identified in this syndrome, a gene which acts in early embryonic development by affecting chromatin structure and gene expression[5].

Choanal atresia, in a child with developmental delay, hypoplastic nipples and scalp defects, has been described in carbimazole/methimazole embriopathy (children born from mother with hyperthyroidism treated with carbimazole/methimazole), the critical period of exposure being 35-38 days[1].

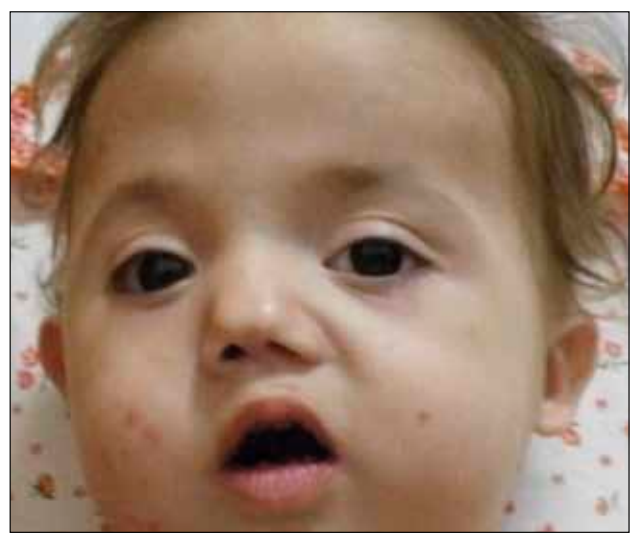

Figure 3 Characteristic aspect of the nose in a child with CHARGE syndrome; note the hypoplasia of the left nostril

3. Abnormal Nasal Bridge

The nasal bridge refers to the region of the nose between the root and the tip (the bony element of the

nose between the orbits)[3]. There is a wide range of normal variation of this nose structure in the normal population, related to some familial traits or specific age variations (e.g. a depressed nasal bridge is very common in infancy)[4].

3.1. Wide nasal bridge

The nasal bridge is defined as wide if there is an increased breadth of the nasal bridge[4].

It is often associated with hypertelorism, like in Down syndrome (Figure 4) or Waardenburg syndrome, a genetic disease characterised by iris heterochromia, hair hypopigmentation and deafness.

Figure 4 Wide nasal bridge in a child with Down syndrome

3.2. High nasal bridge

A high nasal bridge is defined as increased width of the nasal ridge[3]. It is described in Cohen syndrome, a genetic syndrome which associates some dysmorphic features (short philtrum, prominent frontal teeth), developmental delay, truncal obesity, pigmentary retinitis and tapering fingers[4] (Figure 5).

A high nasal bridge is noted also in Wolf-Hirschhorn syndrome (chromosome 4p deletion), together with other characteristic features, including: severe psychomotor retardation, failure to thrive, epilepsy, heart malformation and dysmorphic facial features (Greek helmet aspect) (Figure 6).

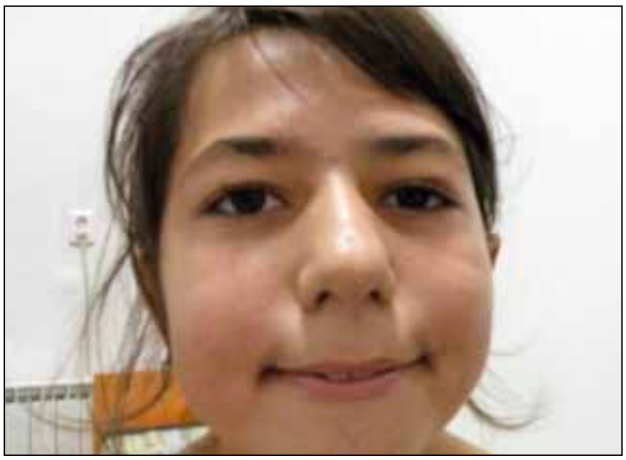

Figure 5 High nasal bridge in a girl with Cohen syndrome

3.3. Flat nasal bridge

Flat nasal bridge is defined as underdevelopment of the bony structure of the nose[4].

This feature is present in Binder syndrome (maxillonasal dysplasia), which associates a maxillary hypoplasia and a flat, vertical nose. The main feature is a hypo-

Figure 6 High nasal bridge and other dysmorphic features (hypertelorism, prominent metopic ridge, preauricular tags, short philtrum, micrognathia) in a child with Wolf-Hirschhorn syndrome.

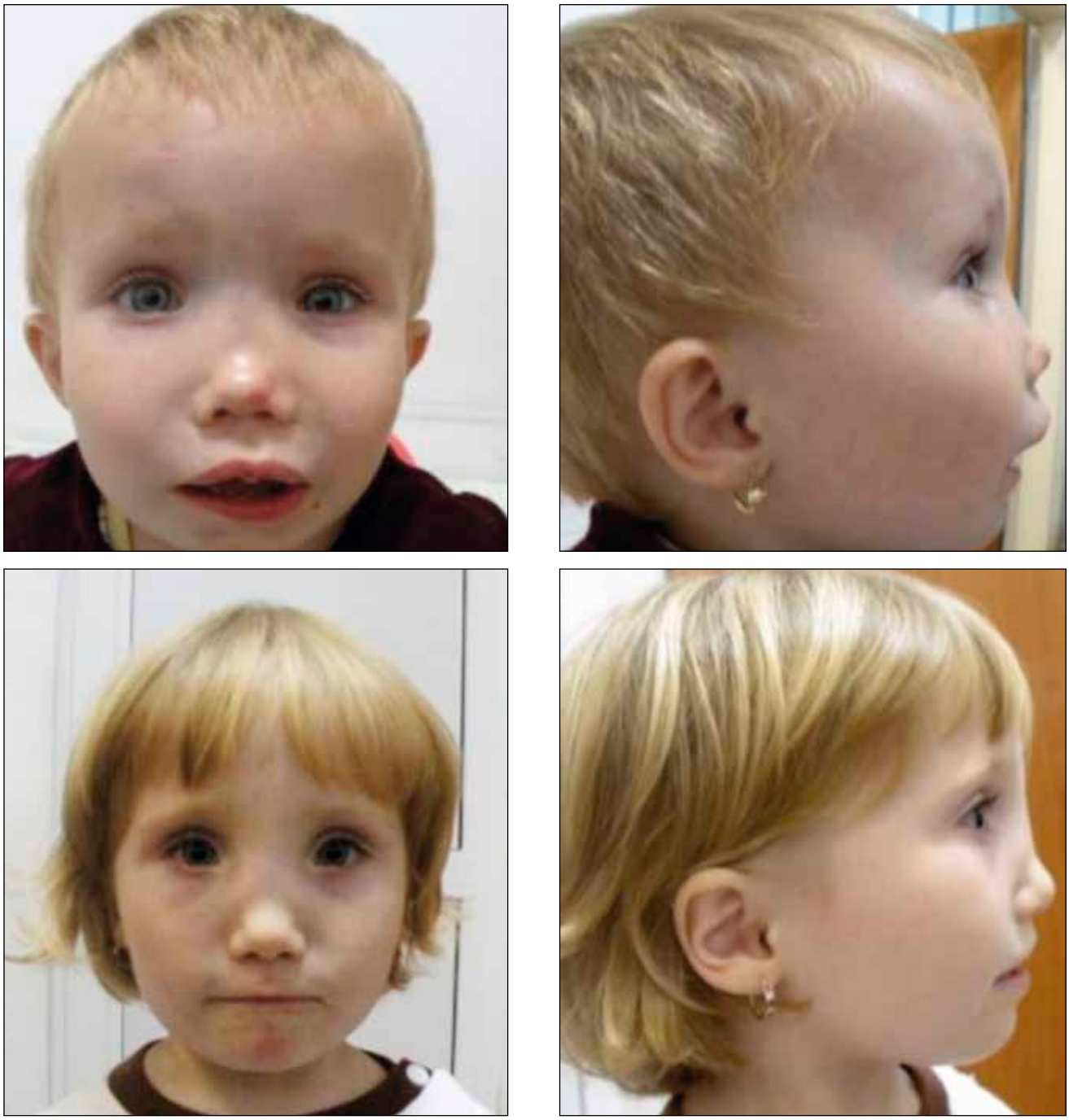

Figure 7 Binder syndrome in two sisters. Note the flat midface, flat nose

plastic nose with flattening of the tip and alae nasi, and absence of the nasal septum/spine[7] (Figure 7).

A flat nasal bridge is also seen in warfarin embryopathy (after exposure of the mother at warfarin or other coumarin derivatives, at 6-12 weeks of gestation), in Stickler syndrome (a genetic disorder of collagen, associating congenital vitreous gel anomaly, myopia, cleft palate, micrognathia, deafness, arthropathy), in X-linked alpha-thalassaemia/mental retardation syndrome (together with other facial dysmorphic features, including tented upper lip, small triangular-shaped nose, and genital anomalies) and in chondrodysplasia punctata (characterised by limb asymmetry and ichthyosis)[4].

3.4. Depressed nasal bridge

Depressed nasal bridge is defined as a posterior positioning of the nasal root in relation to the overall facial profile for age. This feature is described in some genetic syndromes, like Cornelia de Lange syndrome, which also includes other dysmorphic facial features (thick eyebrows with gynophores, long eye-

lashes, short upturned nose, long pilgrim and thin downturned lips) (Figure 8), delayed growth and small stature, psychomotor retardation, limb anomalies, heart malformations. In some cases with Cornelia de Lange syndrome, mutations in the Nipped-B-like gene (NIPBL) on chromosome 5q13 have been reported[4].

A depressed nasal bridge is described in Apert syndrome, associating other facial dysmorphic features (shallow orbits, hypertelorism, downslanting palpebral fissures) (Figure 9), craniosynostosis (brachiocephaly), syndactyly, polydactyly, mental retardation and cerebral malformations. Apert syndrome is caused by a mutation in the fibroblast growth factor receptor-2 gene (FGFR2), on chromosome 10q26[1].

4. Abnormal Alae Nasi

The alae nasi represent the lateral part of the nose forming the outer side of each nostril[3].

4.1. Narrow ala nasi

Narrow ala nasi is defined as slender, slit-like aperture of the nostril[3]. This feature, together with a prominent nasal tip is present in tricho-rhino-phalangeal (TRP) syndrome, associating also a temporally sparse hair, short metacarpals and hypoplastic nails. The syndrome is caused by mutations in the zinc finger transcription factor TRPS1 on chromosome 8q23[1].

4.2. Hypoplastic alae nasi

Hypoplastic alae nasi represent thinned, deficient or excessively arched alae nasi[4].

This feature is described in Johanson-Blizzard syndrome, a genetic syndrome characterised by growth retardation, scalp defects, exocrine pancreatic insufficiency, congenital heart malformation, deafness; the syndrome is caused by mutations in *UBR1* gene on chromosome 15q[6].

Hypoplastic alae nasi, associated with orofacial clefts and lip pits, hypodontia, skin syndactyly and knee webbing/pterygia, is present in Van der Woude syndrome, caused by mutations in the interferon regulatory factor 6 gene on chromosome 1q32[4].

Other genetic syndromes which present hypoplastic alae nasi are: oral-facial-digital type 1, a X-linked dominant syndrome characterised by facial dysmorphis (hypertelorism, downslanting palpebral fissures, low-set ears, broad nasal bridge) (Figure 10), clefts, tongue cysts, excess oral frenulae, syndactyly, brachydactyly, postaxial polydactyly, psychomotor retardation, cerebral malformations, and it is caused by mutations in *OFD1* gene on chromosome Xp22[8]; oculodentodigital syndrome, an autosomal dominant syndrome caused by mutations in GJA1 gene, at 6q22-23 and presenting syndactyly, dental anomalies, neurodegeneration[1].

Figure 8 Depressed nasal bridge in a child with Cornelia de Lange syndrome; also note other characteristic facial dysmorphic features: thick eyebrows with gynophores, long eyelashes, short upturned nose, long pilgrim and thin downturned lips.

Figure 9 Characteristic facial dysmorphism in a child with Apert syndrome, including depressed nasal bridge, shallow orbits, hypertelorism, downslanting palpebral fissures).

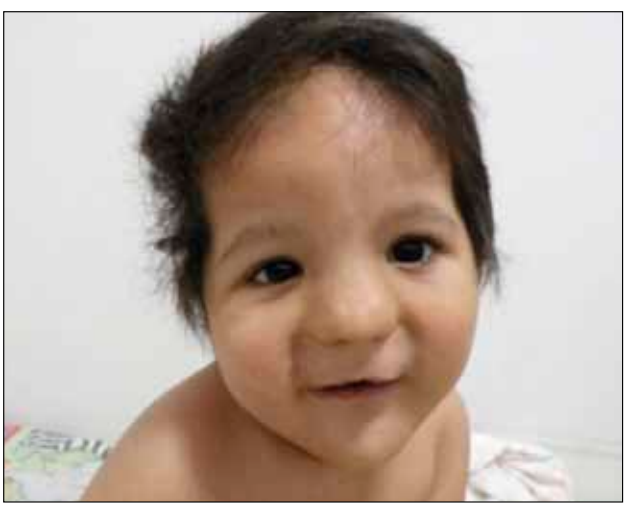

Figure 10 Oral-facial-digital syndrome; note the facial dysmorphic features: hypoplastic alae nasi, hypertelorism, downslanting palpebral fissures, low-set ears, broad nasal bridge.

5. Abnormal nasal tip

The nasal tip represents the most anterior point of the nose.

5.1. Broad nasal tip

This aspect is defined as a prominent, bulbous shape nose; there is an increase in width of the nasal tip. A bulbous nose is described in patients with Williams-Beuren syndrome, which associates other dysmorphic features (periorbital fullness, long philtrum, depressed nasal bridge, anteverted nares, thick lips) (Figure 11), supravalvular aortic stenosis, psychomotor retardation, hypercalcemia[1]. The syndrome is caused by a microdeletion on 7q11.2.

Another genetic syndrome with broad nasal tip is the velocardiofacial syndrome, caused by a deletion on 22q11; other features include short palpebral fissures, wide and prominent nasal bridge and root, small mouth (Figure 12), speech delay, mental retardation, psychiatric diseases, congenital heart malformations, cleft palate, hypocalcaemia and immune defects[3].

A broad nasal tip is also described in tricho-rhino-phalangeal syndrome (see before) and Floating Harbor syndrome, a rare condition characterised by short stature, mild mental retardation, delay of expressive language and a dysmorphic face (deep-set eyes, broad nose, large mouth, low-set ears)[1] (Figure 13).

Figure 11 Broad nasal tip in a patient with Williams-Beuren syndrome; also note other characteristic dysmorphic features: long philtrum, large mouth, thick lips.

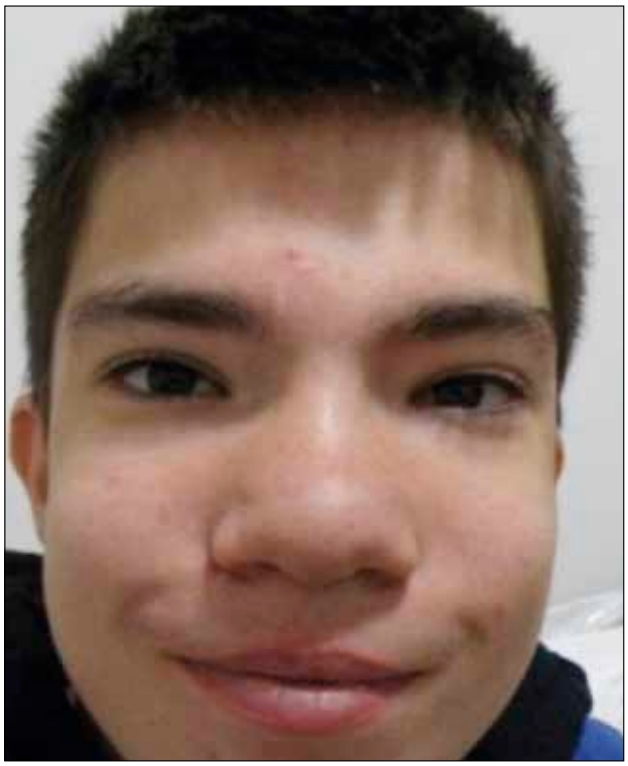

Figure 12 A patient with velo – cardio - facial syndrome, presenting broad nasal tip, short palpebral fissures, wide and prominent nasal bridge and root, low-set ears.

Figure 13 A patient with Floating-Harbor syndrome, showing broad nasal tip, deep-set eyes, broad nose, large mouth.

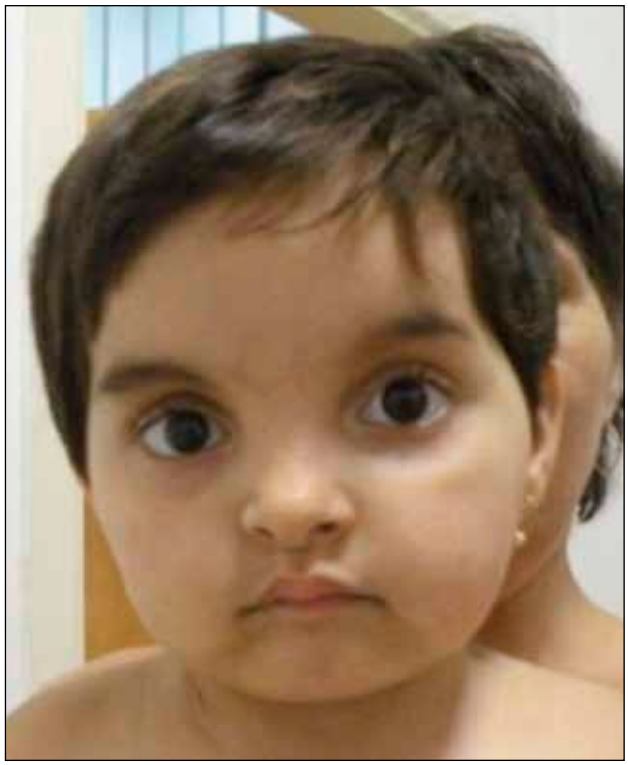

Figure 14 Prominent columella extending below the level of the ala nasi in a patient with Rubinstein-Taybi syndrome.

Figure 15 The prominent nasal columella in a patient with Mowat-Wilson syndrome.

5.2. Bifid nasal tip

This feature is defined as vertical indentation of the nasal tip[2]. It is reported in:

- *frontonasal dysplasia*, a disorder characterised by a midline facial cleft with encephalocele, hypertelorism, bifid nasal tip[1];
- *craniofrontonasal dysplasia*, a X-linked syndrome caused by mutations in ephrin-B1 gene on Xq13.1, which includes coronal synostosis, facial asymetry, ridged nails[9];
- *opitz syndrome*, an autosomal dominant condition, characterised by hypertelorism, cleft lip and/or palate, hypospadias, mental retardation[1];
- *oral-facial-digital syndrome* (see before).

6. Abnormal nasal columella and nares

The columella is the fleshy inferior border of the nasal septum, dividing the nostrils, whose aperture is the nares. It is usually situated at approximately the same level as the alae nasi[2].

6.1. Anteverted nares

Anteverted nares are defined as anteriorly - facing nostril, viewed with the eyes of the observer level with the eyes of the subject[4]. This aspect can be seen in normal subjects, but also can be associated with genetic syndromes, including Cornelia De Lange syndrome, Williams syndrome, Robinow syndrome (associated with hypertelorism and short stature)[4].

6.2. Prominent columella

This feature is defined as increased width of the columella. It is present in Rubinstein-Taybi syndrome, characterised by a prominent beaked nose, downslanting eyes, broad thumbs and first toes, psychomotor retardation, congenital heart malformation; it is caused by genetic anomalies involving *CREBBP* gene on 16p13.3[10] (Figure 14).

A prominent columella is also described in Floating-Harbor syndrome and in Mowat-Wilson syndrome, a disorder characterised by severe developmental delay, microcephaly, epilepsy and constipation, caused by mutation in the zinc finger E box-binding homeobox 2 gene (ZEB2) on 2q22.3[1] (Figure 15).

6.3. Shortening of the columella

This feature is defined as a reduced distance from the anterior border of the naris to the subnasale[2]. It is described in oligohydramnios, as a consequence of fetal constriction, in association with other features like arthrogryposis or cranial asymmetry, in Binder syndrome and in Kabuki syndrome, a disorder caused by a mutation in the myeloid/lymphoid or mixed lineage leukemia 2 gene (MLL2) and characterised by facial dysmorphic features (large prominent ears, long palpebral fissures, eversion of lateral third of lower eyelids, thick eyelashes, depressed nasal tip), psychomotor retardation, congenital

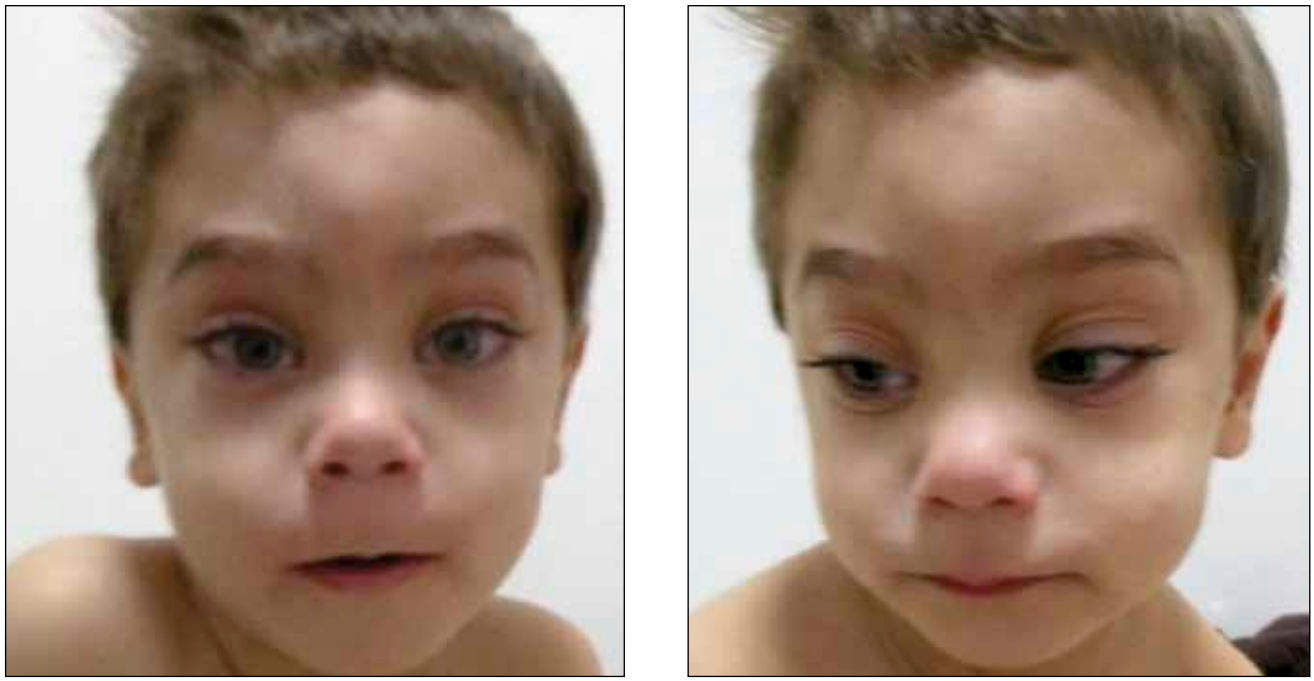

Figure 16 A child with Kabuki syndrome, showing short columella and other characteristic facial features: large prominent ears, long palpebral fissures, eversion of lateral third of lower eyelids, thick eyelashes, depressed nasal tip.

heart malformation and increased susceptibility to infections[1] (Figure 16).

7. Abnormal Nasal Septum

7.1. Beaked nose

This feature is defined as a prominent bridge, giving the nose the appearance of being curved or slightly bent[2]. It is described in[1]:

- Rubinstein-Taybi syndrome;
- Crouzon syndrome, characterised by shallow orbits with exorbitism and a hooked nose; it is caused by mutations of *FGFR2* gene;
- Saethre-Chotzen syndrome, presenting asymmetric coronal suture involvement with facial asymmetry; prominent nose, ptosis, small ears; mutations of the *TWIST* gene have been reported in the majority of patients;
- Majewski osteodysplastic primordial dwarfism II, which includes severe intrauterine growth retardation, beaked prominent nose, progressive hyperextensibilty and bony dysplasia, prominent eyes, small teeth.

CONCLUSIONS

There are very different variations regarding various aspects of the nose. Some of them can be seen in the general population, but other features are specific for some genetic syndromes. In this case, they are associated with other manifestations (dysmorphic features, neuropsychiatric conditions, malformations, etc.), which can help us establish the diagnosis.

REFERENCES

1. Firth H.V., Hurst J.A. (ed). - Oxford Desk Reference Clinical Genetics. Oxford University Press, 2005;p.182-184.
2. Gorlin R.J., Cohen M.M., Hennekam R.C.M. (ed). - Syndromes of the head and neck, 4th edn. Oxford University Press, Oxford, 2001.
3. Hall J.G., Allanson J.E., Gripp K.W., Slavotinek A.M. - Handbook of Physical Measurements. Oxford University Press, 2007.
4. Reardon W. – The bedside dysmorphologyist. Oxford University Press, New York, 2008.
5. Vissers L.E., van Ravenswaaij C.M., Admiraal R., Hurst J.A., de Vries B.B., Janssen I.M., van der Vliet W.A., Huys E.H., de Jong P.J., Hamel B.C., Schoenmakers E.F., Brunner H.G., Veltman J.A., van Kessel A.G. - Mutations in a new member of the chromodomain gene family cause CHARGE syndrome. Nat Genet., 2004;36(9):955-7.
6. Zenker M., Mayerle J., et al. - Deficiency of UBR1, a ubiquitin ligase of the N-end rule pathway, causes pancreatic dysfunction, malformations and mental retardation (Johanson-Blizzard syndrome). Nat Genet., 2005;37:1345-50.
7. Roy-Doray B., Geraudel A., et al. - Binder syndrome in a mother and her son. Genet Couns., 1997;8(3):227-33.
8. Ferrante M.L., Giorgio G., et al. - Identification of the gene for oral-facial-digital I syndrome. Am J Hum Genet., 2001;68:569-76.
9. Twigg S.R.F., Kan R., et al. - Mutations of ephrin-B1 (EFNB1), a marker of tissue boundary formation, cause craniofrontonasal syndrome. PNAS, 2004;101:8652-57.
10. Petrij F., Dauwerse H.G., Blough R.I., et al. - Diagnostic analysis of the Rubinstein-Taybi syndrome: five cosmids should be used for microdeletion detection and low number of protein truncating mutations. J Med Genet., 2000;37:168-76.