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ORIGINAL ARTICLE

List of rare diseases in Bulgaria

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Abstract

Defining and setting a rare disease inventory is a fundamental part of rare disease policy. This tool is of a paramount importance, as it greatly affects the knowledge and awareness of rare diseases not only among health care practitioners, but among all rare disease stakeholders. An official list of rare diseases is particularly beneficial now in the context of the European reference networks for rare diseases, generating added value at both international and local levels.

In this publication, we demonstrate and analyse the establishment of the List of rare diseases in Bulgaria. The Bulgarian experience is a result of a decade-long international collaboration within EU bodies like the Rare Diseases Task Force and the EU Committee of Experts on Rare Diseases, as well as participation in major EU projects, such as RD-Portal (Orphanet), EUROPLAN, EPIRARE, BURQOL-RD, RARE-Bestpractices and RD-Action. Bulgarian rare disease stakeholders applied a transparent, proactive methodology when defining and setting the list. This is a substantial prerequisite for the successful implementation of all ongoing rare disease activities in the country. The described approach could be easily adapted and used in other countries.

Key words

Rare diseases, health policy, centres of expertise, registries, list of rare diseases.

Introduction

Ministerial Ordinance no. 16 on the designation of centres of expertise and on the establishment of a national registry for rare diseases was formally adopted in 2014 in Bulgaria [1]. This document was a result of the input from a working group, consisting of health authorities, clinicians and patient representatives. It legally defined the terms and conditions for designation of local health care providers as centres of expertise for rare diseases, as well as the procedures for establishment of a national rare disease registry. A Commission on Rare Diseases was set up and mandated to monitor and evaluate the implementation of these policies, including the definition of an official list of rare diseases in Bulgaria [1, 2].

The List of rare diseases in Bulgaria is approved and amended by the Minister of Health upon a recommendation by the Commission on Rare Diseases. Apart from the obvious aim to create an inventory for rare diseases, the overall objective of the list is to integrate medical and social approaches to rare disease patients and their families in Bulgaria. This formal catalogue is expected to improve the awareness of and increase the visibility of rare disorders at all levels of the Bulgarian health system. The list is envisaged to greatly influence all rare disease activities in the country. In particular, the National registry of rare diseases, the centres of expertise and reference networks will be defined and operating based on the rare disorders, included in the list [2, 3]. To this date, Italy is the only other country in the EU with an official list of rare diseases, set back in 2001 [4, 5]. In this context, the Bulgarian experience on establishing such a rare disease inventory is important from both methodological and political points of view.

Aim

This publication aims to critically analyze the officially approved List of rare diseases in Bulgaria, its scope and prospects.

Material and methods

We performed a critical analysis on Ministerial Orders RD-01-277 of 27 November 2015 and RD-01-92 of 30 March 2016 that set and supplemented the List of rare diseases in Bulgaria [6,7]. We systematically reviewed the public records of the Commission on Rare Diseases meetings from 2015 and 2016, thus collecting additional information on the list definition, especially the concerns of the Commission when discussing and adopting a recommendation on specific disorders [8]. Search in Medline/PubMed was conducted to identify similar health policies on rare diseases in other EU Member States for comparative analysis.

Results and discussion

Mechanisms for adoption and amendment of the List of rare diseases

The mechanisms for adoption and amendment of the Bulgarian List of rare diseases are regulated by Ordinance no. 16. Any rare disease stakeholder is allowed to submit a disease dossier. The Commission on Rare Diseases formally evaluates it and adopts a recommendation to the Minister of Health, who makes a final decision by issuing an order to amend the list. It is very important to underline that the list is supplemented on a case by case basis. The initially approved version of the list is not closed for modifications [1,2].

A disease dossier must present standardised information, including definition and synonyms, disease classification, epidemiological data, diagnostic criteria, treatment and follow-up protocols, prevention activities if available, proposals for patient access schemes, description of specific local experience and expertise. It is mandatory to present Bulgarian epidemiological data for the condition in question. Once approved for inclusion, this dossier is made publicly available from an open access electronic database [1, 2, 8]. This is a substantial prerequisite for high-quality, equable health care for rare disease patients within the different centres of expertise across the country [9,10].

When included in the list, the conditions are classified according to International Classification of Diseases, 10th revision (ICD-10). In case of a lack of an individual ICD-10 code, the Orphanet code system is applied [11]. Nevertheless, Commission members and local stakeholders have detected some problems using the Orpha codes. For example, non-rare disorders have been assigned an Orpha code [8].

The initial version of the list, recommended by the Commission on Rare Diseases, was approved by the Minister of Health in November 2015 (Ministerial Order RD-01-277). The Commission's proposal was based on the List of conditions, whose outpatient medicinal treatment is reimbursed by the National Health Insurance Fund (NHIF) [12]. This decision was motivated by the presumption that the list should be built upon those conditions, for which there is already established health care infrastructure in the country [13]. Available and accessible medicinal therapy is essential to enhance rare disease health care [14]. The Commission extracted from that list all conditions, which meet the legal definition for a rare disease – prevalence of no more than 5 in 10,000 people. This task was not easy, since local epidemiogical data for rare diseases are virtually missing. There are national disease-specific registries for a very small number of rare conditions [15]. The Orphanet database was generally consulted to determine, if a specific disorder is rare or not [16]. Orphanet was preferred as a decision-making tool over other scientific databases, since it is explicitly mentioned in the EU Cross-Border Health Care Directive [17].

During these initial activities, the Commission gave opportunities for local rare disease stakeholders to take part in the definition of the list. A general call for submission of rare disease dossiers was announced on the websites of the Ministry of Health and NHIF. The Commission sent letters to medical societies and patient umbrella organisations as well. The annual National Conference for Rare Diseases and Orphan Drugs in 2015 provided an additional platform for broad dissemination and consensus building.

Nosological scope of the List of rare diseases

The official List of rare diseases was promulgated by Ministerial Order RD-01-277 in November 2015. This catalogue originally contained 116 rare disorders, listed by ICD-10 code. Ministerial Order RD-01-92 of 30 March 2016 added 18 more rare nosologies to the list (Table 1). By October 2016, 19 more conditions were recommended for inclusion to the List by the Commission and are pending final approval by the Minister of Health [8].

Rare diseases of the blood and blood-forming organs and certain rare disorders, involving the immune mechanism, make more than a half of the list's content (n = 57; 43%). Rare endocrine, nutritional and metabolic conditions (n = 30; 22%) and rare congenital malformations, deformations and chromosomal abnormalities (n = 26; 19%) significantly contributed as well (Figure 1).

The structure of the List of rare diseases in Bulgaria is a logical result of the nature of rare diseases in general. The vast majority of these disorders have a genetic or unknown etiology and predominantly affect infants and children [18, 19]. Furthermore, the content of the list was influenced by the availability and accessibility of orphan therapies. Orphan drug research and development experienced a huge progress in the last decade [20]. New orphan

Table 1. List of rare diseases in Bulgaria by 30 March 2016

No.	ICD-10 code*	Rare disease
1	D55.0	Anaemia due to glucose-6-phosphate dehydrogenase [G6PD] deficiency
2	D56.1/ORPHA231214	Thalassaemia major
3	D56.1/ORPHA231222	Thalassaemia intermedia
4	D58.0/ORPHA822	Minkowski-Chauffard syndrome
5	D59.5	Paroxysmal nocturnal haemoglobinuria [Marchiafava-Micheli]
6	D61.0/ORPHA124	Blackfan-Diamond syndrome
7	D61.0/ORPHA84	Fanconi anaemia
8	D64.4	Congenital dyserythropoietic anaemia
9	D66	Hereditary factor VIII deficiency
10	D67	Hereditary factor IX deficiency
11	D68.0	Von Willebrand disease
12	D68.1/ORPHA329	Hereditary factor XI deficiency
13	D68.2	Hereditary deficiency of other clotting factors
14	D68.2/ORPHA325	Deficiency of factor: II [prothrombin]
15	D68.2/ORPHA326	Deficiency of factor: V [labile]
16	D68.2/ORPHA327	Deficiency of factor: VII [stable]
17	D68.2/ORPHA328	Deficiency of factor: X [Stuart-Prower]
18	D68.2/ORPHA330	Deficiency of factor: XII [Hageman]
19	D68.2/ORPHA331	Deficiency of factor: XIII [fibrin-stabilizing]
20	D68.2/ORPHA335	Deficiency of factor: I [fibrinogen]
21	D69.3	Idiopathic thrombocytopenic purpura
22	D80.0	Hereditary hypogammaglobulinaemia
23	D80.1	Nonfamilial hypogammaglobulinaemia
24	D80.2	Selective deficiency of immunoglobulin A [IgA]
25	D80.3	Selective deficiency of immunoglobulin G [IgG] subclasses
26	D80.4	Selective deficiency of immunoglobulin M [IgM]
27	D80.5	Immunodeficiency with increased immunoglobulin M [IgM]
28	D80.6	Antibody deficiency with near-normal immunoglobulins or with hyperimmuno-globulinaemia
29	D80.7	Transient hypogammaglobulinaemia of infancy
30	D80.8	Other immunodeficiencies with predominantly antibody defects
31	D80.9	Immunodeficiency with predominantly antibody defects, unspecified
32	D81.0	Severe combined immunodeficiency [SCID] with reticular dysgenesis
33	D81.1	Severe combined immunodeficiency [SCID] with low T- and B-cell numbers

Continues →

Table 1. Continued

No.	ICD-10 code*	Rare disease
34	D81.2	Severe combined immunodeficiency [SCID] with low or normal B-cell numbers
35	D81.3	Adenosine deaminase [ADA] deficiency
36	D81.4	Nezelof syndrome
37	D81.5	Purine nucleoside phosphorylase [PNP] deficiency
38	D81.6	Major histocompatibility complex class I deficiency
39	D81.7	Major histocompatibility complex class II deficiency
40	D81.8	Other combined immunodeficiencies
41	D81.9	Combined immunodeficiency, unspecified
42	D82.0	Wiskott-Aldrich syndrome
43	D82.1	Di George syndrome
44	D82.2	Immunodeficiency with short-limbed stature
45	D82.3	Immunodeficiency following hereditary defective response to Epstein-Barr virus
46	D82.4	Hyperimmunoglobulin E [IgE] syndrome
47	D82.8	Immunodeficiency associated with other specified major defects
48	D82.9	Immunodeficiency associated with major defect, unspecified
49	D83.0	Common variable immunodeficiency with predominant abnormalities of B-cell numbers and function
50	D83.1	Common variable immunodeficiency with predominant immunoregulatory T-cell disorders
51	D83.2	Common variable immunodeficiency with autoantibodies to B- or T-cells
52	D83.8	Other common variable immunodeficiencies
53	D83.9	Common variable immunodeficiency, unspecified
54	D84.0	Lymphocyte function antigen-1 [LFA-1] defect
55	D84.1	Defects in the complement system
56	D84.8	Other specified immunodeficiencies
57	D84.9	Immunodeficiency, unspecified
58	E20.0	Idiopathic hypoparathyroidism
59	E22.0	Acromegaly and pituitary gigantism
60	E22.1	Hyperprolactinaemia
61	E22.8	Other hyperfunction of pituitary gland
62	E23.0	Hypopituitarism
63	E23.2	Diabetes insipidus
64	E24.0	Pituitary-dependent Cushing disease
65	E27.1	Primary adrenocortical insufficiency
66	E70.0	Classical phenylketonuria

Continues →

Table 1. Continued

No.	ICD-10 code*	Rare disease
67	E72.2	Disorders of urea cycle metabolism
68	E74.0	Glycogen storage disease
69	E75.2/ORPHA324	Disease: Fabry (-Anderson)
70	E75.2/ORPHA355	Disease: Gaucher
71	E75.2/ORPHA646	Disease: Niemann-Pick
72	E76.1	Mucopolysaccharidosis, type II
73	E76.2	Other mucopolysaccharidoses
74	E80.0/ORPHA79273	Hereditary coproporphyria
75	E80.0/ORPHA79276	Acute intermittent porphyria
76	E80.0/ORPHA79277	Congenital erythropoietic porphyria
77	E80.0/ORPHA79278	Autosomal erythropoietic protoporphyria
78	E80.0/ORPHA79473	Porphyria variegata
79	E80.1	Porphyria cutanea tarda
80	E80.2	Other porphyria
81	E83.0	Disorders of copper metabolism
82	E83.1	Disorders of iron metabolism
83	E83.3	Disorders of phosphorus metabolism and phosphatases
84	E84.0	Cystic fibrosis with pulmonary manifestations
85	E84.1	Cystic fibrosis with intestinal manifestations
86	E84.8	Cystic fibrosis with other manifestations
87	E85.1	Neuropathic heredofamilial amyloidosis
88	G71.0	Muscular dystrophy
89	G71.1	Myotonic disorders
90	G95.0	Syringomyelia and syringobulbia
91	I27.0	Primary pulmonary hypertension
92	J84.1/ORPHA2032	Idiopathic pulmonary fibrosis
93	K50.0	Crohn disease of small intestine
94	M05.0	Felty syndrome
95	M08.0	Juvenile rheumatoid arthritis
96	M08.1	Juvenile ankylosing spondylitis
97	M08.2	Juvenile arthritis with systemic onset
98	M08.3	Juvenile polyarthritis (seronegative)
99	M08.4	Pauciarticular juvenile arthritis
100	M30.0	Polyarteritis nodosa
101	M31.3	Wegener granulomatosis
102	M32.1	Systemic lupus erythematosus with organ or system involvement
103	M32.8	Other forms of systemic lupus erythematosus
104	M33.0	Juvenile dermatomyositis
105	M33.1	Other dermatomyositis
106	M33.2	Polymyositis

Continues →

Table 1. Continued

No.	ICD-10 code*	Rare disease
107	M34.0	Progressive systemic sclerosis
108	M34.1	CR(E)ST syndrome
109	Q21.2	Atrioventricular septal defect
110	Q21.8	Other congenital malformations of cardiac septa
111	Q07.0	Arnold-Chiari syndrome
112	Q20.0	Common arterial trunk
113	Q20.1	Double outlet right ventricle
114	Q20.3	Discordant ventriculoarterial connection
115	Q20.4	Double inlet ventricle
116	Q21.0	Ventricular septal defect
117	Q21.4	Aortopulmonary septal defect
118	Q22.6	Hypoplastic right heart syndrome
119	Q23.0	Congenital stenosis of aortic valve
120	Q25.0	Patent ductus arteriosus
121	Q25.1	Coarctation of aorta
122	Q25.5	Atresia of pulmonary artery
123	Q26.2	Total anomalous pulmonary venous connection
124	Q26.3	Partial anomalous pulmonary venous connection
125	Q81.0	Epidermolysis bullosa simplex
126	Q81.1	Epidermolysis bullosa letalis
127	Q81.2	Epidermolysis bullosa dystrophica
128	Q87.1	Congenital malformation syndromes predominantly associated with short stature
129	Q96.0	Karyotype 45, X
130	Q96.1	Karyotype 46, X iso (Xq)
131	Q96.2	Karyotype 46, X with abnormal sex chromosome, except iso (Xq)
132	Q96.3	Mosaicism, 45, X/46, XX or XY
133	Q96.4	Mosaicism, 45, X/other cell line(s) with abnormal sex chromosome
134	Q96.8	Other variants of Turner syndrome

*ORPHA code is given in cases of no ICD-10 code or an ICD-10 code for a group of disorders.

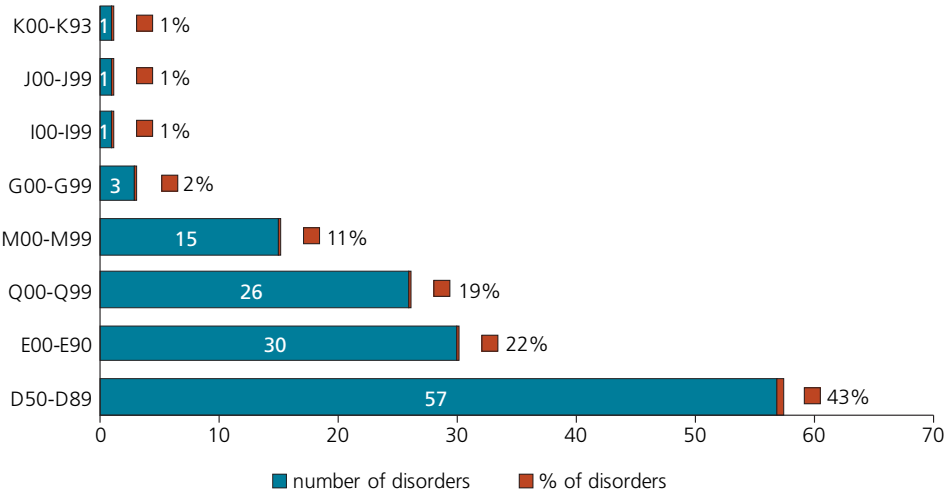

Figure 1. List of rare diseases in Bulgaria by 30 March 2016 by ICD-10 classes.

therapies also mean increased awareness of the indicated rare conditions [21]. Finally, local hematology and medical genetics societies in Bulgaria have been extremely active in rare disease policy making, ensuring effective engagement of these medical professionals in rare diseases.

Examining the public meeting records of the Commission on Rare Diseases showed that only two disorders were rejected for an inclusion [8]. Systemic lupus erythematosus and hidradenitis suppurativa dossiers were negatively assessed because of prevalence exceeding the conventional rare disease threshold. No local epidemiological data were presented in both cases. A Commission decision is currently pending on the dossier of ovarian cancer (ORPHA code 213500). Due to the lack of formal definition of rare cancers, the Commission decided to make a consultation with Bulgarian health authorities and medical societies. Rare diseases and rare cancers do share a lot of commonalities [22, 23]. Having in mind, however, the prospects of the personalised and precise medicine, especially the possibility to fragmentise common cancer nosologies into rare subtypes [24], the Commission considered to explore this issue in depth before making a final recommendation. This decision will set an important precedent in any way with potential significant impact on the national health system.

Conclusion

Defining and setting a rare disease inventory is a fundamental part of rare disease policy. This tool is of a paramount importance, as it greatly affects the knowledge and awareness of rare diseases not only among health care practitioners, but among all rare disease stakeholders. An official list of rare diseases is particularly beneficial now in the context of the European reference networks for rare diseases, generating added value at both international and local levels. We demonstrated and analysed the establishment of the List of rare diseases in Bulgaria. This experience is a result of a decade-long international collaboration within EU bodies like the Rare Diseases Task Force and the EU Committee of Experts on Rare Diseases, as well as participation in major EU projects, such as RD-Portal (Orphanet), EUROPLAN, EPIRARE, BURQOL-RD, RARE-Bestpractices and RD-Action. Bulgarian rare disease stakeholders applied a transparent, proactive methodology when defining and setting the list. This is a substantial prerequisite for the successful implementation of all ongoing rare disease activities in the country. The described approach could be easily adapted and used in other countries.

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Case Report

Beyond appearances: blepharo-cheilo-dontic syndrome. First case in Ecuador

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Abstract

Blepharo-cheilo-dontic (BCD) syndrome comprises the combination of lagophthalmia, euryblepharon, lower eyelid ectropion, distichiasis, cleft lip and palate and oligodontia. This combination has been described as an autosomal dominant condition with variable expression. We herein described an Ecuadorian girl with consistent signs of BCD syndrome. Our patient also has unilateral hearing loss and metatarsus varus. The aim of this paper is to add this case of blepharo-cheilo-dontic syndrome to world casuistry, as it is considered a rare disease.

Key words

Blepharo-cheilo-dontic, cleft lip and palate, euryblepharon, lagophthalmia, ectropion, distichiasis, unilateral hearing loss, metatarsus varus.

Introduction

Rare diseases have a low prevalence in populations. In Europe, a disease is considered rare when it affects 1 in 2,000 people (Eurordis). Rare diseases are characterized by a wide variety of disorders and symptoms that vary not only by disease, but also among patients suffering from the same disease. Research and patient registration is especially essential in making these diseases visible; in many cases, these diseases have been forgotten and may even be completely unknown to most doctors. Blepharo-cheilo-dontic syndrome is an ultra-rare syndrome, with a total of 50 cases reported, as stated by agencies such as Orphanet [1]. The aim of our publication is to add this case of blepharo-cheilo-dontic syndrome to the world casuistry so that it may be considered a rare disease, and it also seeks encouraging physicians to report this type of pathology.

Clinical case

Female newborn, normal birth, with appropriate weight for her gestational age, weight: 2560g, size: 51cm, chest circumference: 31cm, head circumference: 33cm, Apgar 8-9, Capurro 38 weeks of gestation. Physical examination highlights: broad forehead, broad nasal bridge, hypertelorism, ectropion, lagophthalmos, euryblepharon, low-set ears, complete cleft palate (soft and hard), bilateral cleft lip. (Figure 1).

Mother is a 34-year-old housewife from the countryside. Pregnancies: 4, abortions: 1 (third pregnancy, 10 weeks); births: 2, C-section: 1. During this pregnancy, the mother presents: poor weight gain, fetal ultrasound reports low weight, no history of exposure to toxic agents. Father is 37 years old. No consanguinity. No other member of the family has been affected by this disease.

The patient was admitted in the Neonatology Unit for food support, and was discharged without complications within 4 days. The newborn was fed exclusively breast milk. At 8 months old, the patient shows signs of potential hearing loss. At 10 months old, the patient underwent a Millard Repair in order to correct her cleft lip and palate (Figure 2). At 13 months old, traumatology reports show metatarsus varus. The oph-

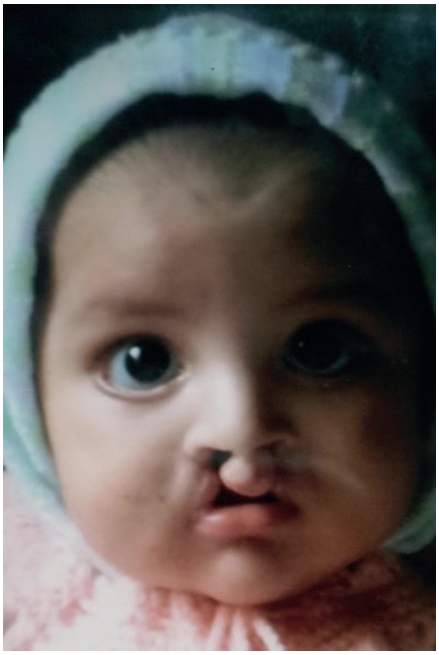

Figure 1. Three months old: euryblepharon and bilateral cleft lip can be identified (with permission from her parents).

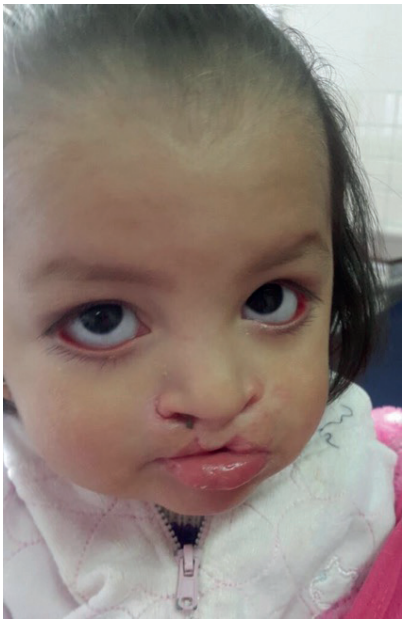

Figure 2. One year old: cleft lip and palate have been corrected. Lagophthalmos is notorious for increasing the euryblepharon (with permission from her parents).

thalmologist recommends artificial tears to prevent corneal laceration (Figure 2).

The patient is currently 18 months old and has been admitted to the pediatrics service multiple times with respiratory infections; last hospitalization was for pneumonia caused by AH1N1, with no complications. It is noted that the patient's teeth are emergent and conical. A comprehensive assessment allowed determining that the clinical manifestations the patient shows are consistent with blepharo-cheilo-dontic syndrome, which was then verified with a genetic analysis, with a normal karyotype.

Discussion

Blepharo-cheilo-dontic syndrome (BCD) (OMIM # 119580) [2] is characterized by the combination of symptoms involving the eyelids, lips and teeth. Blepharo-cheilo-dontic syndrome is a rare autosomal, congenital and dominant condition that includes facial clefting, oligodontia, euryblepharon, lagophthalmos and ectropion [3].

Elschnig (1912) described an association of lower eyelid ectropion, hypertelorism and cleft lip and palate; however, Gorlin et al proposed the term BCD in 1996, though the disease was initially known under the eponym 'Elschnig syndrome'. BCD syndrome has been described in many combinations or included in others such as Miller syndrome, Genée-Wiedemann syndrome or Warburg syndrome [3]. As of 2006, only 32 cases of BCD syndrome have been reported worldwide; in Latin America, Mexico and Brazil are the only two countries with reported cases [4].

From the literature review, it was found that there was no gender predilection in terms of this syndrome [4]. Different combinations of these signs have been found sporadically, with 100% penetration autosomal dominant inheritance [5]. In view of the rarity of the condition, the clinical spectrum is still being delineated and the etiology remains unknown; in our case, the patient was not exposed to toxic agents and did not have a family history of malformations [6].

After considering the clinical similarities between the BCD syndrome and other conditions with ectodermal defects and oral clefts, many observations suggest that mutations in gene p63 and interferon regulatory factor 6 (IRF6) could be implicated as potential candidate genes for BCD syndrome [7].

Other cases with congenital thyroid agenesis and typical findings of BCD syndrome extended the discussion about the genes involved in this syndrome's causes to include thyroid transcription factor 2 (TTF-2 or FOXE1). In humans, one case of a missense mutation in FOXE1 has been found in a case of isolated cleft lip and palate. Recently, two other candidate genes for BCD were described: the odd-skipped-related 2A protein (OSR2) and the T-box-containing protein 10 (TBX10). These genes encode a zinc-finger protein that exhibits a dynamic expression pattern during craniofacial development, primarily in the developing palate and teeth [6].

More recent studies focus on the importance of gene Dlx4. In mammals, there are three Dlx homeobox clusters with closely located gene pairs (Dlx1/Dlx2, Dlx3/

Dlx4, Dlx5/Dlx6). In situ hybridization showed that Dlx4 is expressed in the mesenchyme of the murine palatal shelves at E12.5, prior to palate closure. From the published literature, Dlx1/Dlx2 double homozygous null mice and Dlx5 homozygous null mice both presented clefts in the secondary palate. A DLX4 mutation in a family with cleft lip and palate establishes DLX4 as a potential cause of human clefts [8].

Patients with autosomal dominant blepharo-cheilo-dontic (BCD) syndrome have mainly eye, dental and limb anomalies [9].

Eye anomalies include: lower lid ectropion, distichiasis of the upper eyelids, euryblepharon, hypertelorism and lagophthalmia [3]. Upper eyelid distichiasis is the presence of a double row of eyelashes. Lagophthalmia is a condition in which the eye cannot be completely closed because the palpebral fissures are wider than normal [2]. Euryblepharon suggests that once the eyelid is everted in the uterus, for some reason, orbicularis spasms act as a sphincter that leads to secondary venous engorgement and chemosis; until this cycle is broken, the eyelid will not assume its normal position [10]. Our patient was born with mild eye abnormalities, but these increased with facial growth.

Oral anomalies include cleft lip and palate (most often bilateral), conical teeth, hypodontia, oligodontia and/or microdontia. Oligodontia has been found in three quarters of the cases reported, whereas conical teeth have been noted in less than half [2]. The sites of missing teeth in mild oligodontia cases were adjacent to the cleft of the lip. Micro-retrognathia was reported in 5 cases [4].

Other sporadic symptoms that have been reported in patients with this disorder include clinodactyly, syndactyly [7, 9], hypothyroidism, imperforate anus [11] and hearing loss [6], as reported in our case, though there have been some cases of BCD syndrome with dermal symptoms such as sparse scalp hair and hypoplastic nails [4]. However, no cases for BCD syndrome have been reported with metatarsus varus or joint deformities, as is the case of this patient.

No individual had potentially fatal symptoms. Growth and development were normal in all reported patients [4]. The clinical manifestations in our patient are similar to other cases of BCD reported in literature, presenting normal physical and intellectual development.

Treatment should be comprehensive, focused on repairing facial deformities with proper functionality [12].

For ocular deformities, lateral tarsal strip repairs, eyelid retraction and lateral tarsorrhaphy were performed. Appropriate reconstructive surgery of the eyelids reduces the morbidity associated with eyelid anomalies and provides an excellent cosmetic result for patients with blepharo-cheilo-dontic syndrome [13]. Removal of the horizontal laxity of the eyelid is needed for managing ectropion; however, vertical shortage of the eyelid remains and lagophthalmos never disappears [10].

The use of overdentures, a conservative approach for cases of severe maxillary hypoplasia, severe hypodontia and cleft lip and palate, is well documented. Overdentures can readily restore function, appearance, soft tissue deficit and re-establish positive occlusion, as the prostheses replace both the tissue and missing teeth, increase vertical facial height and result in an overall improvement in appearance [12].

Conclusions

All typical symptoms of blepharo-cheilo-dontic syndrome such as euryblepharon, lower eyelid ectropion, bilateral cleft lip and palate, and conical teeth were observed in our patient. For this patient, this study recommends a long and active treatment plan with a multi-disciplinary team that may address all areas of development.

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Case Report

Fetal hepatic mesenchymal hamartoma. A case report

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Informed consent
Informed consent form was duly signed by the parents of the newborn regarding acceptance for investigation and publication

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Abstract

Hepatic tumors accounted 5% of congenital neoplasms. Mesenchymal hamartoma of the liver is a rare benign childhood tumor, whose definitive diagnosis during the fetal period remains difficult, despite advances in antenatal imaging. In this paper, we report a case of hepatic mesenchymal hamartoma diagnosed prenatally with ultrasound scan showing a multicystic mass in the left upper abdomen accompanying polyhydramnios and complicated by a preterm labor. The newborn died on the first day of life due to respiratory distress and neonatal jaundice. The diagnosis was confirmed histologically post-delivery.

Key words
Hepatic mesenchymal hamartoma, fetal ultrasound scan, prenatal diagnosis.

Introduction

Mesenchymal hamartoma of the liver (MHL) is an extremely rare benign childhood tumor, whose etiology remains unclear. Described for the first time in 1956 by Edmondson [1], MHL is an uncommon benign hepatic tumor that in 80% of cases is detected during the first two years of life [2]. Despite advances in antenatal imaging have allowed accurate and earlier diagnosis of MHL during the fetal period, a definitive diagnosis of this tumor in utero remains difficult. In fact, including the current case, there have been only 20 reported cases of MHL diagnosed or detected prenatally by ultrasound examination [3]. Although this lesion is histologically benign, its rapid growth to enormous size may result in perinatal complications such as fetal hydrops, maternal toxemia, preterm labor and intrauterine fetal death.

We report a case of hepatic mesenchymal hamartoma diagnosed prenatally with ultrasound scan showing a multicystic mass in the left upper abdomen accompanying polyhydramnios and complicated by a preterm labor. The diagnosis was confirmed histologically after delivery.

Case report

A 34-year-old pregnant women, gravida 3 para 2, was referred to our unit at 33 weeks of gestation for management of her pregnancy. An antenatal ultrasound showed a highly vascularized intra-abdominal anechoic cyst, occupying two-third of the abdominal cavity and pumping up the intestine associated with polyhydramnios. Since cyst was compressing other organs and distending abdomen, a termination of pregnancy has been proposed but refused by the couple. At 34 weeks of gestation, the pregnancy was complicated by a preterm labor and a male newborn of 2600 g was vaginally delivered. The examination of the newborn showed an abdominal firm lump. Postnatal X-chest radiograph showed a compression of both lung fields by the abdominal mass. The newborn died on the first day of life due to respiratory distress and neonatal jaundice. Postmortem abdominal ultrasound noted an anechoic cyst, measuring 13 cm, in close relation to the left lobe of liver. A complete autopsy was performed and the external examination showed a male neonate anatomically of 34-35 weeks having

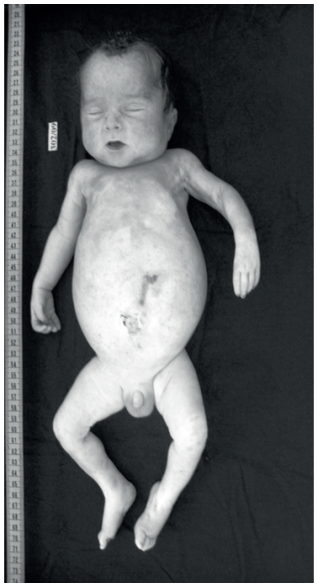

Figure 1. External examination: male neonate anatomically of 34-35 weeks with an abdominal dilatation and a venous collateral circulation (with permission from his parents).

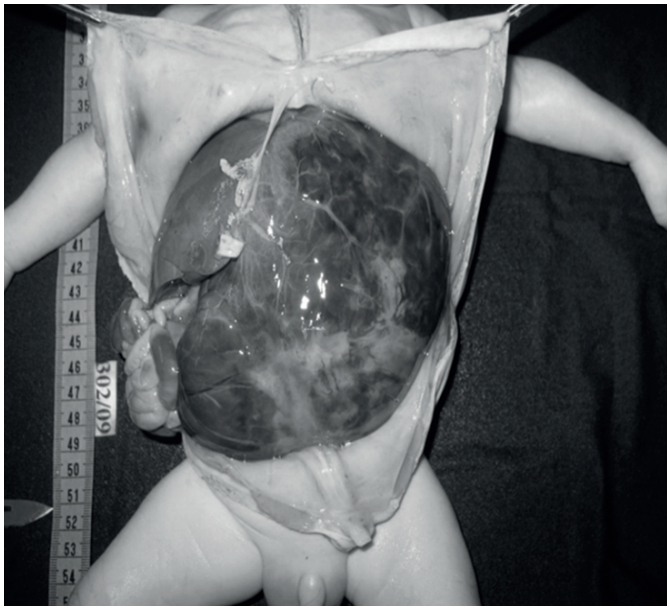

Figure 2. Macroscopic examination: hepatic tumor of the left lobe showing bleeding reshuffle (with permission from his parents).

an increased periumbilical diameter, an abdominal dilatation and a venous collateral circulation (Figure 1). Fetal dissection noted an ascites, a splenomegaly, a pulmonary hypoplasia, a pleuro-pericardial effusion, and a cardiomegaly. The liver weighted 383.7 g (normal: 60 g) and was the seat of a well limited tumor developed in the left lobe and measuring 14 cm, with hemorrhage and necrosis (Figure 2). Histologically, the tumor showed a mixture of normal liver tissues with blood or lymphatic vessels, bile ducts within an abundant edematous and myxoid stroma (Figure 3). The histopathology description confirmed the diagnosis of a mesenchymal hamartoma of the liver. The histological examination of the placenta was not done.

Discussion

Primary hepatic tumors are rare in children, where they account for about 5% of all intra-abdominal masses and represent between 0.5% and 2% of all pediatric neoplasms [4]. Mesenchymal hamartoma of the liver (MHL) is the second most common benign hepatic tumor in children [4], defined as an excessive focal overgrowth of mature normal cells and stroma native to the liver [5] and presents as a large, rapidly growing mass during early infancy [6]. A strong female predisposition for fetal MHL was reported, and this is in contrast with the male preponderance for postnatal MHL [2]. Microscopically, MHL consists of spindle cells in a myxoid background, with occasional areas of extramedullary hematopoiesis, all in a disordered arrangement of mesenchyme, malformed bile ducts, and cords of normal-appearing hepatocytes [4]. Cytogenetically, these tumors are characterized by translocations involving 19q13.4 [4].

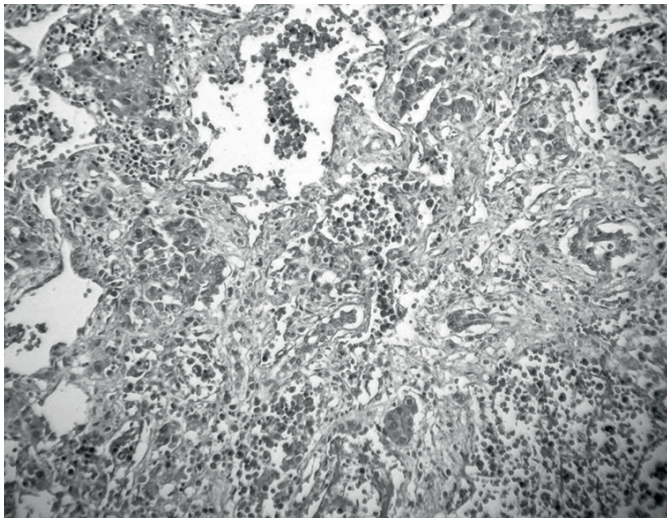

Figure 3. Histopathology examination: mixture of normal liver tissues with blood or lymphatic vessels, bile ducts within an abundant edematous and myxoid stroma.

Even with advance prenatal diagnostic tools, prenatal diagnosis of MHL remains challenging because the hepatic origin can be difficult to be specified in ultrasound examination. MRI can be useful to identify liver tissue, which is the only organ to produce a hyperintense signal on T1 imaging [7, 8]. In our case, the prenatal diagnosis of MHL was not made because the origin of the cystic intra-abdominal masse was uncertain. Usually, prenatal ultrasound detects MHL during the last trimester of pregnancy with a mean gestational age at 35 weeks [4, 9]. The MHL presented prenatally as multicystic and hypovascular masses, but mixed

and solid lesions were also described. In the largest series by Isaacs [9], 45 cases of mesenchymal tumors are reported over a period of 35 years. However, only 14 cases were prenatally diagnosed in this series and most common presentation was abdominal cyst with a mean gestational age of 35 weeks. Since the differential diagnosis is very difficult to do because the natural history of the tumor is still not known, only pathological findings after surgical resection is the cornerstone in the definition of the mass [10].

Although this lesion is histologically benign, associations with congenital heart disease, intestinal malrotation, biliary atresia, omphalocele, myelomeningocele, Beckwith-Wiedemann syndrome, and abnormalities of chromosome 19 have been reported [2, 4, 5]. While the MHL has generally a good prognosis in childhood, the outcome is much worse when diagnosed in the prenatal period with a mortality rate of 35% [2, 9, 11]. In our case, the liver tumor was diagnosed at 33 weeks of gestation and was associated with a polyhydramnios and a compression of the lungs. Prenatal occurrence of these tumors is associated with adverse outcome mainly due to its mass effects. Poor prognostic factors are mainly represented by the early onset of presentation, the rapidly progressing tumor, and the polyhydramnios [6, 7, 12]. Congestive cardiac failure reported in case of MHL is due to the compression of the inferior vena cava and umbilical vein [11]. The risk of hydrops is increased by the loss of fluid to the cysts and the reduced liver production of fetal albumin [11]. Polyhydramnios is associated with upper intestinal tract obstruction and elevation of the diaphragm poses the fetus at risk for pulmonary hypoplasia.

Invasive antenatal procedures remain controversial and a balanced consideration in a multidisciplinary team is mandatory in each individual patient. In the literature, some authors proposed intrauterine cyst drainage [7] since the risks of simple or repeated needle aspiration appear minimal compared to the consequences of a large fetal abdominal mass. Tsao et al. [6] suggested that the goal of the treatment with repeated aspirations was to reduce the lesion to a manageable size providing adequate decompression to allow for proper placental and fetal organ development and safe vaginal delivery. However, other authors demonstrated that the drainage of the cyst fluid do not reduce the production of cyst fluid, firstly because the fluid would have reaccumulated in the cyst [13, 14] and, secondly, because multilocular cysts frequently have no communication with each other [13, 15]. Thus, antenatal therapy is only decompressive and does not reduce the need for postnatal surgical resection which offers definitive diagnosis and treatment. The surgical treatment should have as purpose to reduce the production of cyst fluid using a complete resection when possible or partial resection and cauterization of the cyst wall adherent to hepatic parenchyma if complete excision of the tumor is dangerous or invasive [11].

Conclusion

Despite technological advancements and efforts toward early diagnosis, the prognostic of the MHL remains poor due to mass effects and associated fetal malformations. Actually, no firm recommendations can be made about the mode of delivery of the fetus with a presumed MHL, and the invasive antenatal procedures remain controversial. Thus, several publications are still needed to establish a consensus for optimum management.

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