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Agnathia-otocephaly complex: a case report and a literature review on recurrence risk

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Abstract

Objectives: Agnathia-otocephaly complex (AOC) is an extremely rare, lethal disorder causing obstruction of the upper airway at birth due to absence of the mandible and hypoplasia of the oral cavity. Implications for future pregnancies need to be elucidated by parental counselling, as recurrence of AOC or associated comorbidities are possible. Very little is known on this subject, because of the rarity of the disorder and scarce data on genetic causes of this complex. The objectives of this study were to determine the recurrence risk and mode of inheritance for AOC based on current literature.

Contents: Recurrence of AOC or associated comorbidities within the family of an index case was reported in eight articles, describing 7 and 27 relatives, respectively. There were eight AOC cases in which the genetic cause was known. Mutations in 2 genes, orthodenticle homeobox 2 (OTX2) and paired related homeobox 1 (PRRX1), have been described. Due to its mainly sporadic appearance, recurrence risk is low. Counselling on recurrence risk is difficult, because of a broad heterogeneity with complex inheritance patterns and variability in phenotypic expression.

Outlook: Chromosomal analysis and exome sequencing in children with AOC will help unravel current aetiological uncertainties and could help in further reproductive decisions. We emphasize the need for timely diagnosis through ultrasound, providing parents with the opportunity

to receive multidisciplinary counselling, giving them the chance to contemplate their management decisions.

Keywords: agnathia-otocephaly complex; foetal anomaly; parental counselling; recurrence risk.

Introduction

Agnathia-otocephaly complex (AOC) is an exceptionally uncommon congenital developmental defect. It is marked by (1) hypoplasia or absence of the mandible (agnathia), (2) underdevelopment of the oral orifice (microstomia) and (3) ventral and horizontal positioning of the ears (melotia) with or without midline fusion (synotia). This triad results in an obstruction of the upper airway, with a high risk of mortality. Unless an artificial airway is created, death shortly after birth is imminent. Prenatal diagnosis by ultrasound is possible; however, often the pathology is only recognized late during pregnancy, leaving parents in pressing need of guidance in informed decision making [1]. After having lost a child, parents often fear reoccurrence of events during future pregnancies. Information on the topic of the aetiology and recurrence risk is scant, rendering counselling difficult.

In this report we present a new case of AOC and give a brief literature review to estimate recurrence risk and to clarify the mode of inheritance for some AOC cases on the basis of the current genetic knowledge.

Case presentation

A 29 year-old woman was referred to our centre at a post-menstrual age of 25 weeks 0 days because of polyhydramnion and facial abnormalities in the foetus. It was the firstborn of non-consanguineous parents, the pregnancy had been uneventful and the non-invasive prenatal testing (NIPT) at 12 weeks gestation was normal. Ultrasound showed severe hypoplasia of the mandible and central fusion of the ears. Counselling regarding the high risk of mortality because of the obstructive airway was provided. The parents opted for termination of pregnancy,

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Figure 1: Anterior and lateral images showing microstomia, synotia and agnathia.

but before a decision by the ethical committee, the mother went into spontaneous preterm labour.

She delivered a boy with a weight of 645 g (25th percentile), a length of 34.5 cm (80th percentile) and a head circumference of 22.7 cm (45th percentile). The child had Apgar scores of 2 and 1 after 1 and 5 min. Clinical examination showed a midfacial protuberance containing a cranially displaced nose and very small oral orifice (proboscis), caudally displaced orbitae with down-slanting palpebral fissures in a hypoteloric position as well as horizontally and medially displaced ears fusing on the midline (Figure 1). The mandible was absent and there was no air entry on auscultation.

The parents opted for a non-active management. The child was placed skin-to-skin with his mother and was given analgesia. The boy died of respiratory failure shortly after birth. Psychological support was delivered to the parents. Besides the facial abnormalities, autopsy showed hypoplasia of the lungs, turbid cornea and atretic external auditory canals. The internal organs were found to be normal, as well as the genitalia and extremities. Microarray CGH analysis was done and was found to be normal (array CGH 46, XY). Mendeliome analysis on 6210 genes couldn't find an explanation for the phenotype. Gene analysis of paired related homeobox 1 (PRRX1) and orthodenticle homeobox 2 (OTX2) did not show mutations. The parents were counselled for a probably low recurrence risk. Expertise ultrasound surveillance during a following pregnancy was suggested.

Materials and methods

We conducted a retrospective literature study in February 2020, searching the PubMed/Medline database using

following search words or Mesh terms: [otocephaly], “agnathia otocephaly complex”, “isolated agnathia” or “dysgnathia complex”. We looked for English articles on human cases of AOC, without imposing restrictions on publication dates. The articles were screened for inclusion, first by abstract, then by full text, if available. As a definition of AOC, we used the presence of the clinical triad of mandibular hypoplasia/agnathia, microstomia and melotia/synotia. Attention was made that cases were only enlisted once. We collected data on sex, time of diagnosis, gestational age at diagnosis, gestational age at birth, termination of pregnancy, associated comorbidities, genetic studies and recurrence of AOC or comorbidities in the family. Because this was a retrospective literature search, permission of the Ethical Commission was emitted.

The goal of this work was to delineate the AOC population and to get insight into the underlying genetic causes and recurrence within the family. With this information, parental counselling can be optimized.

Results

Our search yielded 100 results, of which 43 articles were found to be relevant. Twenty-four items were unattainable. By screening of the reference lists of the 43 articles, we were

Table 1: Characteristics of cases with AOC.

Characteristics of cases with AOC			
Sex	41 girls	45 boys	11 N.A.
Type of AOC	22 isolated	65 associated comorbidities	10 N.A.
Time of diagnosis	50 prenatally	17 at birth	30 N.A.
Termination of pregnancy	21 yes	16 no	8 N.A.

AOC, agnathia-otocephaly complex; N.A.: information not available.

able to include another 14 reports. A total of 97 cases were identified. Table 1 lists the most important characteristics of the population.

There is a slight uneven distribution of boys and girls. In 22/87 (25.2%) AOC was isolated, whereas 65/87 (74.7%) had associated comorbidities, with holoprosencephaly being the most common. In 17 patients (25.3%), the congenital anomaly was unanticipated and was discovered at birth, at a mean gestational age of 29w6d. The diagnosis was made prenatally in 50 pregnancies (74.6%), at a mean gestational age of 23w3d. Respectively 5, 39 and 16 subjects were diagnosed during the first (0d–12w6d), second (13w0d–26w6d) and third ($\geq 27w0d$) trimester of pregnancy. If we set the cut-off at 24w0d, the ethical boundary of viability in Belgium, 25/50 of the prenatal diagnoses were made $< 24w0d$, the other half $\geq 24w0d$ (results not shown in table). Termination of pregnancy was opted in 28/50 (56%) subjects when a prenatal diagnosis was made. There were 2 events of parents opting for termination of pregnancy, but due to legislation in the country of origin it was not completed.

Table 2 shows the genetic defects that have been described in AOC cases and in known recurrent cases of AOC or other comorbidities within family. Associated malformations are described.

Of the 97 AOC cases, eight had a genetic defect reported. Out of 58 karyotype analyses, one unbalanced translocation between chromosomes 6 and 18 was found [2].

There were three patients with mutations in the *PRRX1* gene [6–8] and 4 with a genetic defect in the *OTX2* gene [12–13], with all mutations leading to a loss-of-function of the processed protein. In the majority of cases there were no results of genomic screening, because of unavailable DNA of the probands and/or family members.

Recurrence of AOC in siblings or other family members was described in six articles [2–5, 9, 10, 13]. Occurrence of associated comorbidities in relatives, ranging from micrognathia, ophthalmological abnormalities to sensorineural hearing loss, was described in six articles [5, 9–13]. In 9 family members across three families with associated comorbidities, mutations in *OTX2* were shown. One *de novo* mutation in *PRRX1* was found in a sibling with micrognathia [10].

Various types of associated malformations on top of AOC were found: holoprosencephaly and other neurological malformations, skeletal deformities, cardiac malformations, urinary tract malformations, gastro-intestinal malformations, ophthalmological abnormalities and dermatological abnormalities.

Discussion

AOC (OMIM #202650; also known as dysgnathia complex, agnathia-holoprosencephaly, otocephaly) is a very rare congenital anomaly with an incidence of less than 1 in 70.000 births. A defect in blastogenesis causes the first branchial arch to fail to develop into the lower jawbone, parts of the ear and the anterior two-thirds of the tongue [1]. Often, comorbidities such as holoprosencephaly, ophthalmologic abnormalities, situs inversus or skeletal deformities are associated [1, 7, 13]. The ventral position of the ears differentiates the anomaly from other syndromic pathologies such as Treacher Collins syndrome, Goldenhar, Pierre Robin sequence or Nager syndrome [10]. Few children have been known to survive the perinatal period and needed extensive reconstructive surgery, aside from tracheostomy and gastrostomy feeding [1].

The aetiology of this birth defect is still an area of research. Teratogens, such as amidopyrine, salicylates and theophylline have been reported [10] and could account for discordance in phenotypes of monozygotic diamniotic twins with AOC [14]. Most reported cases occurred sporadic; although a few familial cases are known, indicating a genetic background. A clear inheritance pattern, however, could not yet be established.

Since 2011, mutations have been found in two genes that are involved in and co-operate on the normal organogenesis of the first branchial arch development: *PRRX1* and *OTX2* [9, 10, 13]. Apart from craniofacial organization, *PRRX1* and *OTX2* are involved in regulation of central nervous system, eye and limb development [6]. This discovery has started to shed some light upon the aetiological mechanisms behind AOC.

Genetic mutations in AOC cases

Most of the AOC cases were sporadic, as was previously found in the literature [1]. However, a few causative mutations have been found to date (Table 2). We note 1 translocation, three variations in the *PRRX1* gene and four *OTX2* mutations in AOC patients.

The translocation between chromosomes 6 and 18 described by Pauli et al. [2] and Krassikoff et al. [3] was the only karyotypical anomaly we came across. Chromosome 18 has been involved in other craniofacial anomalies in the past, such as premaxillary agenesis or hypoplasia of the tongue and mandible [15].

Our search identified two dominant *de novo* mutations in *PRRX1* [6, 7] and one autosomal recessive mutation in

Table 2: Overview of genetic defects in AOC and recurrence in family members.

Author, year	Genetic defect in AOC index case	Recurrence of AOC/associated comorbidities & genetic defect in relatives	Type of AOC (isolated vs. associated malformations)
Pauli, 1983 [2] Krassikoff, 1989 [3] Porteous, 1993 [4]	Unbalanced translocation: 46,XX, der18, t(6;18) (p24.1;p11.2)pat No genetic testing done	1 sibling with AOC: no genetic testing done 1 sibling with AOC: no genetic testing done	Index case: AOC + holoprosencephaly Sibling: AOC + holoprosencephaly Index case: AOC + other malformations: Cutis aplasia, absent right eyelids, distal arthrogryposis, brachydactyly, syndactyly (2/3) and displacement of the fourth toes, imperforate anus, absent falx cerebri, asymmetric frontal bones, flat skull base, cerebellar hypoplasia, malformation of the truncus arteriosus, VSD, malrotation, hypoplastic right kidney and absent left kidney, single umbilical artery Sibling: AOC + other malformations: Distal arthrogryposis, displacement of the fourth toes, imperforate anus Index case: AOC + other malformations: Imperforate anus Sibling: AOC + other malformations: Retroflexion of sacrum
Rust, 1999 [5]	Normal male karyotype, 46,XY	1 sibling with AOC: normal female karyotype. Mother with micrognathia & melotia: no genetic testing done	Index case: AOC + other malformations: Anal atresia, partial renal agenesis and skeletal defects
Sergi, 2011 [6]	Normal karyotype. De novo heterozygous point mutation in exon 2 of <i>PRRX1</i> leading to a missense mutation with loss-of-function (p.Phe113Ser)	Not assessed	Index case: Isolated
Donnelly, 2012 [7]	Normal karyotype. De novo heterozygous c.267delA frameshift mutation in exon 2 of <i>PRRX1</i> leading to loss-of-function (p.Lys90Argfs*131)	Not assessed	Index case: AOC + other malformations: ASD
Çelik, 2012 [8]	Normal karyotype. Homozygous mutation in exon 4 of <i>PRRX1</i> , leading to a missense mutation with loss-of-function (p.Ala231Pro)	Not assessed; parents consanguineous	Index case: AOC + other malformations: ASD
Chassaing, 2012 [9]	No genetic testing done	1 sibling and a third cousin with AOC: no genetic testing done 18 other family members with micro-/anophthalmia +/- micrognathia: c.316delC mutation in exon 3 of <i>OTX2</i> in 7/18 family members with associated comorbidities (other 11 no genetic testing done)	Index case: N.A.

Table 2: (continued)

Author, year	Genetic defect in AOC index case	Recurrence of AOC/associated comorbidities & genetic defect in relatives	Type of AOC (isolated vs. associated malformations)
Dasouki, 2013 [10]	No genetic testing done	1 sibling with AOC: no genetic testing done 1 sibling with micrognathia: <i>de novo</i> heterozygous c.266_269dupAAAA mutation in exon 2 of <i>PRRX1</i>	Index case: N.A.
Akiyama, 2013 [11]	No genetic testing done	1 sibling with micrognathia, mother with left anophthalmia-left sensorineural hearing loss: no genetic testing done	Index case: Isolated
Patat, 2013 [12] (Case 1)	De novo deletion 14q23.1, whole <i>OTX2</i> gene deleted	Not assessed	Index case: AOC + other malformations: club feet
Patat, 2013 [12] (Case 4)	Normal karyotype. Autosomal dominant mutation in <i>OTX2</i> gene, leading to a nonsense mutation with loss-of-function (p.Arg97*)	4 generations of microphthalmia (maternal), c.289C>T nonsense mutation in <i>OTX2</i> (p.Arg97*) in mother	Index case: AOC + other malformations: Microphthalmia, absence of optic chiasm and pituitary gland, brachymesophalangy of the fifth finger and bilateral talus valgus
Sergouniotis, 2015 [13]	Autosomal dominant duplication mutation in exon 4 of <i>OTX2</i> (p.Gln91dup)	1 sibling with AOC and 1 sibling with micrognathia: Heterozygous duplication mutation in exon 4 of <i>OTX2</i> (p.Gln91dup) in both siblings	Index case: N.A.

AOC, agnathia-otocephaly complex; ASD, atrial septal defect; N.A.: information not available.

PRRX1 inherited from both parents, who were heterozygous carriers [8]. Çelik et al. [8] state that genetic testing only identifies a mutation in *PRRX1* in less than 15% of the AOC cases. In our observations, there was a mutation in *PRRX1* in three out of 97 AOC cases, but genomic testing was not performed in most cases.

Patat et al. [12] and Sergouniotis et al. [13] presented three causative variations in *OTX2*: 2 were inherited autosomal dominantly and 1 was a *de novo* mutation. Sergouniotis et al. [13] reported that 40% of the *OTX2* mutations were *de novo*. Our, however very limited, study results show one *de novo* mutation in three.

Results of mutation analysis for *PRRX1* and *OTX2* in respectively three and four other AOC patients remained negative [12, 16–18]. This suggests that mutations in these two genes can only partially explain the aetiology of the pathology. Since craniofacial development and formation of the branchial arches is a complex mechanism involving multiple genes, it is probable that other, currently unknown genes might play a role. Other aetiologies such as non-genetic (i.e. teratogenicity) or multifactorial/polygenic might also play a role [1, 14].

Recurrence

Recurrence of AOC and/or associated symptoms within the same family has been published in eight articles (Table 2).

The recurrence of agnathia-otocephaly was observed in seven family members across six families [2–5, 9, 10, 13]. Among the recurrent AOC cases there was only 1 causative mutation found, in *OTX2* [13]. Recurrence of associated comorbidities, such as micro- and anophthalmia, micrognathia, hearing loss or learning disabilities, was seen more often: 27 relatives across six families were described [5, 9–13]. Mutations in *PRRX1* and *OTX2* were found in two and nine patients, respectively [9, 10, 12, 13].

Looking at families with multiple affected cases, it is striking that mutations in *OTX2* can present as heterogenic phenotypes. We illustrate with 2 examples.

Sergouniotis et al. [13] describe a family with a first child with AOC that died in the perinatal period, a second child with AOC for whom pregnancy was terminated at 17 weeks, a third micrognathic child and their asymptomatic father. There was no genomic sequencing done for the first child. All three of the other subjects were screened and were shown to share the same mutation: a heterozygous duplication mutation in exon four of *OTX2*, even though they present with different phenotypes.

Second, Chassaing et al. [9] note a single frameshift mutation in seven family members, caused by a deletion in

exon three of *OTX2*, resulting in different physical characteristics, varying from isolated microphthalmia, anophthalmia with/without intellectual disability. For the other 14 affected subjects (3 with AOC, 11 with ophthalmological and/or mandibular developmental defects) further genetic testing wasn't performed.

Mutations in *OTX2* have been known to present as many different phenotypes: AOC, a variety of ophthalmological abnormalities, a spectrum of mandibular developmental defects from slight micrognathia to agnathia, pituitary anomalies, short stature, learning disabilities, mental retardation or even combinations. In *OTX2* mutations, variable expressivity and incomplete penetrance have been previously documented, and the role of modifier genes has been implied [9, 12, 13]. Together with different modes of inheritance (*de novo*, recessive, dominant) and possible polygenic and/or multifactorial aetiology, these findings illustrate the genetic complexity behind AOC.

Prenatal diagnosis

Lastly, this literature review has shown that the diagnosis of AOC is often made rather late, with 25% of cases (17/67) only being discovered at birth. In 50% of the cases (25/50), prenatal diagnosis was made after the ethical limit of viability. However, the mandible should be visible on ultrasound starting late in the first trimester [1, 19]. Gekas et al. [1] report that the absence of the mandible frequently remains unnoticed, and that more often AOC is discovered incidentally when associated malformations are found by ultrasonography. Isolated AOC has often been missed. Therefore, in case of difficult visualization of the mandible on two-dimensional ultrasound, further investigations are necessary. Three-dimensional ultrasound, CT and MRI have been implemented successfully [1]. In our 97 cases, use of 3D ultrasound was only noted 16 times. We note, however, that 3D ultrasound was not available in all cases, due to early publication dates. Timely diagnosis allows parents to receive counselling and gives them time to consider the options in management, either therapeutic or termination of pregnancy.

Conclusions

Agnathia otocephaly complex is a severe congenital, lethal defect that is often diagnosed late during pregnancy, or even only at birth.

This literature searches uncovered 97 cases of AOC, most of them with a sporadic appearance. We found eight articles describing recurrence of AOC or associated

symptoms within families, such as ophthalmological abnormalities and other forms of mandibular developmental defects. We were able to identify 8 cases of AOC with an underlying genetic defect. Because AOC mainly occurs sporadic, recurrence risk is low. The broad heterogeneity with complex inheritance patterns and variability in phenotypic expression continues to make an estimation of recurrence risk very difficult.

In the future, we hope to have a better understanding of the underlying mechanisms causing AOC, their inheritance pattern and the recurrence risks. Further studies with exome/genome sequencing will probably shed more light on these questions. We recommend sequencing of *PRRX1* and *OTX2* in cases of AOC.

Finally, we would like to emphasize the importance of early prenatal diagnosis of AOC. Visualization of the mandible is described to be possible on ultrasound from 12 weeks gestational age and upward. In case of doubt, 3D ultrasound, or even MRI or CT imaging can be used as confirmation [1, 10]. An early diagnosis could lead to prompt multidisciplinary counselling, allowing parents to contemplate further management.

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