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

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,
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 (probroscis), 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). Mendelome 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 the following search words or Mesh terms: [otocephaly], “agnathia otocephaly complex”, “isolated agnathia” or “dysagnathia 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 able to add 9 articles. PubMed search terms were [otocephaly] and [agnathia].

Table 1: Characteristics of cases with AOC.

| Characteristics of cases with AOC | Sex | Type of AOC | Time of diagnosis | Termination of pregnancy |
|----------------------------------|-----|-------------|-------------------|--------------------------|
|                                  | 41 girls | 22 isolated | 50 prenatally     | 21 yes                   |
|                                  | 45 boys  | 65 associated comorbidities | 17 at birth | 16 no                   |
|                                  | 11 N.A.  | 10 N.A.     | 30 N.A.           | 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 (≥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 ≥24w0d (results not shown in table). Termination of pregnancy was opted in 28/50 (56%) made <24w0d, the other half ≥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 sensineural 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 neurologica 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, otoccephaly) 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 causatives 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] | Unbalanced translocation: 46,XX, der18, t(6;18) (p24.1;p11.2)pat | 1 sibling with AOC: no genetic testing done | Index case: AOC + holoprosencephaly  
Sibling: AOC + holoprosencephaly |
| Porteous, 1993 [6] | No genetic testing done | 1 sibling with AOC: no genetic testing done | 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 |
| Rust, 1999 [5] | Normal male karyotype, 46,XY | 1 sibling with AOC: normal female karyotype. Mother with micrognathia & melolcia: no genetic testing done | Index case: AOC + other malformations: Imperforate anus  
Sibling: AOC + other malformations: Retroflexion of sacrum |
| Sergi, 2011 [6] | Normal karyotype. De novo heterozygous point mutation in exon 2 of PRRX1 leading to a missense mutation with loss-of-function (p.Phe1135Ser) | Not assessed | Index case: AOC + other malformations: Anal atresia, partial renal agenesis and skeletal defects |
| Donnelly, 2012 [7] | Normal karyotype. De novo heterozygous c.267delA frameshift mutation in exon 2 of PRRX1 leading to loss-of-function (p.Lys90Argfs*131) | Not assessed | Index case: Isolated |
| Çelik, 2012 [8] | Normal karyotype. Homozygous mutation in exon 4 of PRRX1, 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-/anophtalmia +/- micrognathia: c.316delC mutation in exon 3 of OTX2 in 7/18 family members with associated comorbidities (other 11 no genetic testing done) | Index case: N.A. |
| 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: de novo heterozygous c.266_269dupAAAA mutation in exon 2 of *PRRX1* | Index case: N.A. |
| Akiyama, 2013 [11] | No genetic testing done | 1 sibling with micrognathia, mother with left anophthalmia-left sensineural hearing loss: no genetic testing done | Index case: Isolated |
| Patat, 2013 [12] (Case 1) | De novo deletion 14q23.1, whole *OTX2* gene deleted | Not assessed | Index case: AOC + other malformations: club feet |
| Patat, 2013 [12] (Case 4) | Normal karyotype. Autosomal dominant mutation in *OTX2* gene, leading to a nonsense mutation with loss-of-function (p.Arg97*) | 4 generations of microphthalmia (maternal), c.289C>T nonsense mutation in *OTX2* (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 *OTX2* (p.Gln91dup) | 1 sibling with AOC and 1 sibling with micrognathia: Heterozygous duplication mutation in exon 4 of *OTX2* (p.Gln91dup) in both siblings | Index case: N.A. |

AOC, agnathia-otocephaly complex; ASD, atrial septal defect; N.A.: information not available.
**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 counseling 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 sporadically, 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 \textit{PRRX1} and \textit{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 early as 12 weeks of gestation. \textit{Agnathia-otocephaly} complex: description of four cases and consideration of the role of \textit{PRRX1} and \textit{OTX2} in cases of AOC.

Research funding: None declared.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Authors state no conflict of interest.

Ethical approval: The local Institutional Review Board deemed the study exempt from review.

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