Two families with Axenfeld-Rieger Syndrome, a case series describing clinical findings, treatment of the dental anomalies and dentofacial deformities and a review of the current clinical findings and genetic knowledge.

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Abstract

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TITLE PAGE

Two families with Axenfeld-Rieger Syndrome, a case series describing clinical findings, treatment of the dental anomalies and dentofacial deformities and a review of the current clinical findings and genetic knowledge.

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ABSTRACT

A descriptive retrospective review of two Danish families with Axenfeld-Rieger Syndrome. Documenting clinical findings, treatment of the dental anomalies and dentofacial deformities is described. This article demonstrates the importance of early diagnosis, referral and treatment in highly specialized center to receive the best outcome.

KEY CLINICAL MESSAGE

Early diagnose and treatment is important to reduce risk of blindness and to initiate early treatment of dentofacial abnormalities to improve functional and aesthetic outcome. A highly specialized multidisciplinary team is advisable.

KEYWORDS

Axenfeld-Rieger syndrome, dental anomalies, maxillofacial anomalies, craniofacial anomalies.

INTRODUCTION

Axenfeld-Rieger syndrome (ARS) is a rare autosomal dominant disorder with complete penetration and variable expressivity (1). The first description of the inherited syndrome was in 1935 by Rieger (2, 3). Different estimated incidence has been described 1:200.000 (2), 1:50.000 to 1:100.000 (1). 70% of the cases are inherited and 30% are arising de novo (4). ARS has variable expressivity and it is considered to be a heterogeneous disorder both morphologically and genetically (2, 3, 5). There is not reported any racial or sexual predilection (6, 7) and the syndrome has been described in different ethnic groups, including Asia, Middle East, South and North America, Africa and Europe (1).

ARS is a combination of anterior chamber cleavage syndrome and nonocular abnormalities (8). Since 1989 (9) the term ARS has been used collectively for, Axenfeld's syndrome, Axenfeld's anomaly, Rieger's anomaly and Rieger's syndrome (10). An overview is giving in table 1 with a description of the different anomalies and syndromes according to Bender et al. (10). ARS is characterized as a syndrome with malformation of the anterior segment of the eye in combination with a wide spectrum of non-ocular abnormalities such as dental, craniofacial and somatic abnormalities. The wide range of clinical presentation and developmental disturbances is described by many authors in the literature (2-8, 11, 12) and is listed in table 2. Hypodontia and failure of the periumbilical skin to involute is most frequently seen (3, 7, 8). A change in the periumbilical skin can be wrongly diagnosed as umbilical hernia and lead to unnecessary surgery (1).

Pathogenesis of ARS is assumed to be a genetic failure that results in development disturbance in the late gestation period. A defect in the ectodermal tissue due to a change in migration and differentiation of the neural crest tissue is thought to be the cause (8, 9). The neural crest cells are responsible for the formation of the craniofacial and ocular structures including bones, cartilage, dental papillae, pituitary gland and the umbilical ring (7). ARS is in the literature (1, 13) divided in to three different types, due to different genetic mutations and deletions (14, 15) combined with different ocular and systemic expressions see table 3.

The aim of this study is to present to two families with Axenfeld-Rieger Syndrome, present their clinical findings, treatment of the dental anomalies and dentofacial deformities.

MATERIAL AND METHOD

Editorial policies and ethical considerations

An approval from the data comity was achieved VC-2019-71 and the patients signed an informed consent allowing clinical photos to be published. The study follows the Declaration of Helsinki.

Case series

At the Department of Oral and Maxillofacial Surgery, Copenhagen University Hospital, Rigshospitalet, we treated and followed four patients in two Danish families, in the period 1987 to 2019. The patients were initially referred from private dental practice, dental school and the public dental healthcare, all with functional and aesthetic problems, due to malocclusion and reduced chewing function caused by missing teeth and/or broken prosthetics.

Patient files and radiographs were reviewed concerning dental and craniofacial anomalies, likewise the treatment performed. Common to all patients was multiple agenesis and class III malocclusion due to hypoplastic and retrognathic maxillae. Considering treatment all patients were treated by a multidisciplinary team of surgeons, orthodontists and prosthodontists. Three out of four patients had a corrective Le Fort 1 osteotomy. All had bone augmentation from mandibular ramus or iliac crest simultaneously with placement of dental implants. After the healing period fixed oral rehabilitation was performed. In table 4 a full description of the patient's clinical and radiographical manifestations and treatment is listed.

All patients were followed in the years after treatment, implant follow up between 1 and 13 years. Only one implant was lost prior to loading and the patient received a fixed dental bridge instead, due to the wish of patient of no further surgeries. All the patients are satisfied with the treatment both aesthetically and functionally. The patients are all presented as 4 separate cases with clinical and radiographic findings and follow up, see figure 1, figure 2, figure 3 and figure 4.

DISCUSSION

In patients with ARS it is described (9) that 43% showed dental abnormalities and 24 % had facial anomalies but not all patients show the same manifestations of abnormalities and anomalies. The different clinical presentation is probably due to pleiotropic genes affecting the tissues derived from neural crest cells (16), making it a morphologic and heterogeneous syndrome. There are many different strategies and opinions on the timing and planning for correction of the skeletal anomalies and missing teeth, this force individual planning in each patient.

In the literature there is, in general an agreement on the importance of a specialized team for planning and treatment each individual patient, due to ARS being a syndrome with a wide phenotypic heterogeneity.

Early diagnosis and treatment planning both concerning the dentofacial appearance and function but also more crucial diagnosing systemic abnormalities. Missing or delaying diagnosis of abnormalities in the ocular aspect could increase the risk of a patient to become blind due to missing prophylaxis and/or postponed initialized treatment. The diagnosis is made based on the clinical and ophthalmologic examination, and if ARS is suspected a genetic analyze can be performed.

The treatment plan is depending on a good interdisciplinary team of ophthalmologist, geneticist, maxillofacial surgeon, orthodontist and prosthodontist, working as a highly specialized team. Relative to the dentofacial deformity, early treatment in childhood or early adolescence, in terms of adaptive growth treatment, eg. Hugo De Clerck type of treatment could possibly benefit the patients (17).

GeneticsGenetic loci have been described to have association with ARS: FOXC1, Forkhead box protein C1, on chromosome 6p25. PITX2, Pituitaryn Homeobox 2, on chromosome 4q25. PAX6, on chromosome 11. A fourth locus had been found on chromosome 13q14 but the gen is not identified yet (2). FOXC1 mutations are often associated with patients with ocular abnormalities, hearing and heart defects (10), 50-75% of patients with the mutation will develop glaucoma (18). There is 54 known mutations of FOXC1 gene including missense (n=31), nonsense (n=6) and deletions, duplications, frameshift, insertions (n=17) (19). The mutations alter the function of FOXC1 by alteration in the gene structure, nuclear localization, DNA-binding capacity, transactivation activity, DNA-binding specify and protein stability. Point mutations are found to be the most common (20). PITX2 mutations are associated with ocular and systemic abnormalities (10). PITX2 is an activator for genes (DIX2) that are essential in teeth and craniofacial development (5, 10). There is 87 known mutations of PITX2 gene including missense (n=33), nonsense (n=10), splice-site (n=6) and deletions/insertions/duplications (n=38) (1). The expression and function of FOXC1 and PITX2 is collected in Table 5 due to (21), (22)

(2) found that 40 % of the patients had a mutation in PITX2. A mutation in PITX2 and FOXC1 is estimated to be responsible for 40% of the cases of ARS (10). As stated earlier in table 3 there is a correlation between the mutations and the type of ARS.

CONCLUSION

Only the beginning of the cell biology and molecular genetics is being understood and 60% of the genetic basis of ARS in still unknown. Early diagnose is important due to initiate early treatment hereby reduce the possible effect of the anterior chamber changes and postpone or hopefully avoid blindness. Because of the high incidence of glaucoma, it is crucial to follow the patients frequently and monitor the intraocular pressure and the appearance of the optic nerve. Likewise, it is important to initiate early treatment of dental and facial abnormalities to improve functional and aesthetic outcome. As the care of the patients is complex it is advisable to have highly specialized multidisciplinary team to diagnose and treat this patient group.

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TABLES

Table 1: Combination of anomalies and syndromes in Axenfeldt Riegers Syndrome

Table 2: Possible clinical findings in patients with Axenfeldt Riegers Syndrome

Table 3: Types of Axenfeldt Riegers Syndrome

Table 4: Treatment and clinical findings in the presented four cases

Table 5: Expression and function of genes resulting in Axenfeld Riegers Syndrome

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