International Journal of Paediatric Dentistry 2005; **15:** 459–463

Dental anomalies in Axenfeld–Rieger syndrome

E. M. O'DWYER & D. C. JONES
Department of Oral and Maxillofacial Surgery, Arrowe Park Hospital, Upton, UK

Summary. The authors describe the case of a 10-year-old girl presenting with Axenfeld–Rieger syndrome (ARS), a rare autosomal dominant condition. The patient showed severe hypodontia, microdontia and short roots. Early diagnosis of the syndrome from its dento-facial and systemic features is important so that subsequent ocular complications may be prevented.

Introduction

Axenfeld–Rieger syndrome (ARS) is a rare autosomal dominant condition. It incorporates features of the Axenfeld and Rieger syndromes, indicating that both these conditions are variable expressions of the same gene abnormality. The syndrome is characterized by deranged or arrested development of neural crest cells in the anterior chamber of the eye, facial bones, teeth, periumbilical skin and cardiovascular system. Early diagnosis of the syndrome from its dento-facial and systemic features is important since subsequent ocular complications may be prevented. A case presenting in a 10-year-old girl is described.

Case report

A 10-year-old female with missing teeth was referred by her dentist to the Department of Oral and Maxillofacial Surgery, Arrowe Park Hospital, Upton, UK. She was the second child of noncosanguinous parents.

Axenfeld–Rieger syndrome had been diagnosed by comprehensive ophthalmic examination when the subject was 3 years old. This was performed because of the strong family history of glaucoma. Her mother had undergone a trabeculectomy, surgery to reduce intraocular pressure by creating an alternative drainage channel for aqueous humour. Clinical examination revealed that the girl had the facial features of ARS, including mild malar hypoplasia and hypertelorism (Fig. 1).

Correspondence: D. C. Jones, Department of Oral and Maxillofacial Surgery, Arrowe Park Hospital, Arrowe Park Road, Upton, Wirral CH49 5PE, UK. E-mail: emilymodwyer@hotmail.com

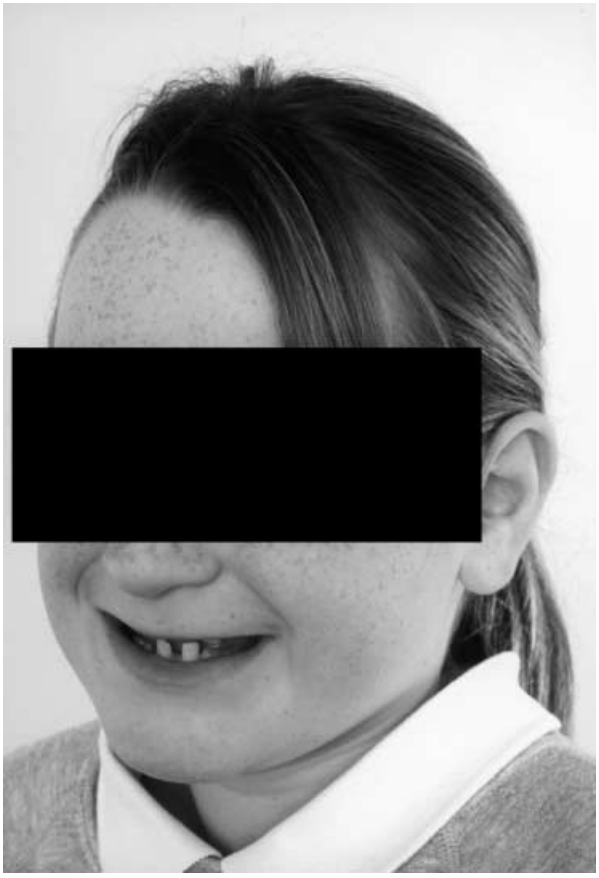

Fig. 1. Lateral facial photograph.

Intraorally, the subject presented with a retained primary dentition demonstrating gross attrition (Figs 2 & 3). The teeth which were present included 16, 55, 54, 51, 62, 63, 64, 65, 26, 31, 73, 74, 75, 36, 37, 41, 43, 84, 85, 46 and 47. An orthopantomogram

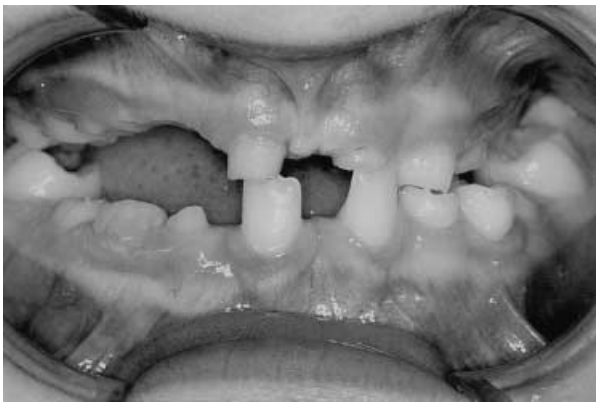

Fig. 2. Frontal occlusion photograph showing a retained primary dentition, diastema and a bilateral maxillary posterior cross-bite.

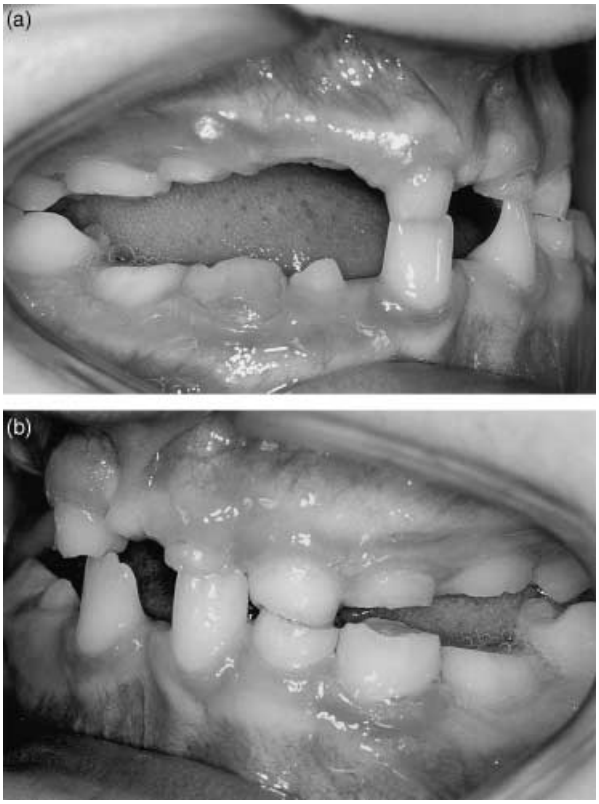

Fig. 3. (a & b) Lateral occlusion photographs.

revealed severe hypodontia. (Fig. 4). Unerupted teeth included 17, 14, 24, 25, 33, 34 and 44, with an unerupted, rudimentary upper right second premolar (15). In total, 15 permanent teeth (18, 13, 12, 11, 21, 22, 23, 27, 28, 32, 35, 38, 42, 45 and 48) were absent (Table 1). All first permanent molars and lower second molars were *in situ*, with the upper left canine and lower left first premolar partially erupted.

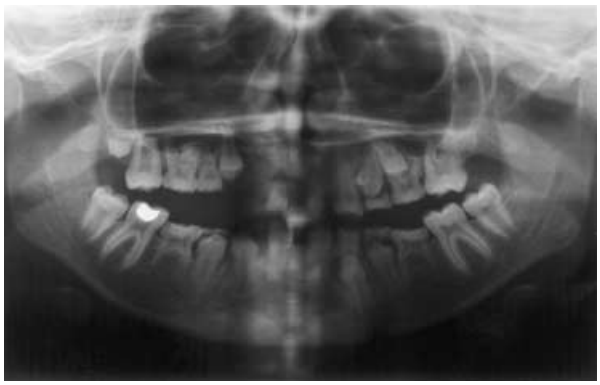

Fig. 4. Orthopantomogram displaying severe hypodontia with absent central and lateral incisors, and lower second and upper right premolar. NB Tooth 15 is rudimentary.

Table 1. Chart of the subject's teeth which were recorded as present, unerupted or missing using the Zsigmondy–Palmer and FDI systems.

Variable	Teeth
Zsigmondy–Palmer system	
Present	6 E D A | B C D E 6
	7 6 E D 3 1 | 1 C D E 6 7
Unerupted	7 5 4 | 4 5
	4 | 3 4
Permanent teeth missing	8 3 2 1 | 1 2 3 7 8
	8 5 2 | 2 5 8
F.D.I. system	
Teeth Present	16, 55, 54, 51 | 62, 63, 64, 65, 26
	47, 46, 85, 84, 43, 41 | 31, 73, 74, 75, 36, 37
Teeth	17, 15, 14 | 24, 25
Unerupted	44 | 33, 34
Permanent teeth missing	18, 13, 12, 11 | 21, 22, 23, 27, 28
	48, 45, 42 | 32, 35, 38

No other permanent teeth were identified. This severe hypodontia with missing central and lateral incisors and second premolars is characteristic of ARS. All teeth were microdont and had short roots.

The patient remains under review in a specialist paedodontic clinic and may require extensive oral rehabilitation when growth of the cranio-facial skeleton is complete. This will comprise of a multi-disciplinary team approach involving the general dental practitioner, the restorative dentist, the orthodontist, and the oral and maxillofacial surgeon.

Discussion

History

Vossius first documented bilateral anterior chamber defects of the eyes associated with hypodontia

in 1883. In 1820, Karl Axenfeld, an ophthalmologist, described the syndrome as 'a white line in the posterior aspect of the cornea and tissue strands from the periphery of the iris to this line' [1]. Herwigh Rieger described Axenfeld's findings plus changes in the iris, stromal atrophy, pupillary abnormalities and nonocular development defects as an inherited condition in 1935 [2,3].

The incidence of ARS is estimated at one per 200 000 of the population [4]. It is an inheritable developmental disorder with complete penetrance and variable expression [1,2]. Inheritance is autosomal dominant in 70% of cases with 30% of cases arising *de novo* [4,5]. Grosso *et al*. 2002 described cases with overlapping phenotypes which demonstrate high 'intrafamilial variability'. When diagnosing a syndrome, this variability can cause confusion since the classic features may not be expressed.

Clinical features of the Rieger ocular anomaly and the Axenfeld anomaly

According to Jorgenson, an anomaly is 'a specific defect' [7]. The Rieger ocular anomaly and the Axenfeld anomaly are both disorders of embryological development of the anterior chamber of the eye alone. They are known as anterior chamber cleavage syndromes [1].

Glaucoma and visual loss occurs in 60% of all children who are diagnosed with the Rieger or Axenfeld anomalies [2]. The anterior chamber angle abnormalities in the Rieger anomaly, Axenfeld anomaly and ARS are parts of the spectrum of a single disorder with a broad overlapping phenotype [8].

Rieger syndrome

A syndrome refers to 'commonly associated defects' or 'a recognized pattern of malformations' [7].

Rieger syndrome includes ocular features, such as goniodysgenesis (a developmental aberration of the anterior ocular segment), with dental, craniofacial and skeletal defects. The extraocular features which are consistent include hypodontia and failure of the periumbilical skin to involute [7,9]. The dental manifestations of Rieger syndrome differentiate it from other ocular syndromes, such as the Peter anomaly, the Rieger anomaly, juvenile glaucoma or the Axenfeld anomaly [10]. Associated conditions are learning difficulties, cerebellar hypoplasia, conduction deafness, limb malformations, hypospadias in males and congenital heart defects [9,11].

Shields *et al*. discussed the difficulty differentiating the Axenfeld and Rieger anomalies clinically, and proposed the collective term Axenfeld Riegers Syndrome (ARS) for all variations within this spectrum of disorders [1]. Axenfeld–Rieger syndrome illustrates three clinical expressions of the same gene [7]. Patients have 'a bilateral developmental disorder of the eyes, autosomal dominant inheritance, no sex predilection, frequently nonocular developmental defects and a high incidence of secondary glaucoma' [1].

Aetiology of Axenfeld–Rieger syndrome

It has been suggested that ARS is a result of damaged or abnormally migrated neural crest cells, the ectodermal mesostroma, late in gestation [12]. Neural crest cells are responsible for initiating craniofacial, dental and ocular development. This results in underdeveloped associated neural crest tissues, i.e. the dental and facial bones.

Clinical features of Axenfeld–Rieger syndrome

Table 2 describes the clinical features of ARS. These patients often have maxillary hypoplasia (not observed in this case, see Fig. 1), prominent supraorbital ridges, telecanthus, a broad nasal bridge, and a protrusive lower and recessive upper lip [13]. An empty or enlarged sella turcica has also been described. Hypodontia may result in an underdeveloped maxillary alveolus at the site of the missing teeth, resulting in a reduced occlusal face height [14]. In a study by Ozekis in 1999, 43% of patients with ARS had dental anomalies, while 25% had facial anomalies [15].

Mathias first reported the dental anomalies in 1936 [1]. The oral manifestations of ARS vary: These patients exhibit microdontia, hypodontia, enamel hypoplasia and taurodontia. Central incisors, lateral incisors and second premolars are frequently microdont or missing [4,13]. The case described here had some absences in the permanent dentition.

Genetic features

The ARS chromosomal abnormality has been linked to loci at chromosomes 4q25, 6p25, 13q14, 16q24 and 11. Two genes, FOX-C1 and P1TX2, on chromosomes 4q25 and 6p25 have been identified [16,17]. Mutations in the P1TX2 coding sequence lead to various phenotypes of ARS and other anterior

Table 2. Clinical manifestations of Axenfeld–Rieger syndrome.

Condition	Clinical manifestation
Ocular	Axenfeld anomaly Rieger ocular abnormality (as described) goniodysgenesis Glaucoma
Cranio-facial	Maxillary hypoplasia/prognathic profile Mandibular hypoplasia Hypertelorisim Prominent supraorbital ridges Telecanthus Broad nasal bridge Protrusive lower lip/recessive upper lip Enlarged sella turcica
Dental	Hypodontia Hypoplasia Taurodontia Microdontia Hyperplastic frena
Associated systemic conditions	Failure of periumbilical skin to involute Cerebellar hypoplasia Conduction deafness Vertebral/limb malformations Hypospadias Congenital heart defects Myotonic dystrophy Scoliosis Kyphosis Lipodystrophy Inguinal hernia Sternum abnormalities Kidney malformations Retarded bone growth

ocular segment malformations [17]. It has been suggested that the Dlx2 gene expression is a regulator of branchial arch development and plays a role in tooth morphogenesis in patients with ARS [18].

Management

Patients with ARS require regular ophthalmic appointments to monitor intraocular pressure and optic nerve head changes throughout their lives so that glaucoma can be diagnosed. Since the syndrome is frequently familial, blood relatives should also be investigated. Over 50% of patients with ARS develop secondary glaucoma, which poses the threat of visual loss and blindness.

The initial therapy for glaucoma is medical, and involves the topical application of alpha-agonists, beta-blockers or carbonic anhydrase inhibitors in an attempt to decrease intraocular pressure [1]. Surgical intervention is required in the majority of patients, and this includes goniotomy (a procedure whereby an opening is made in the skin blocking the drainage gap of the eye, thus providing a passage for aqueous fluid to flow out of the eye and reduce intraocular pressure), trabeculectomy (a passageway/drainage tube in the sclera, hidden under the upper eyelid, by which the aqueous fluid inside the eye can escape to lower the intraocular pressure) and trabeculotomy (a piece of tissue in the drainage angle of the eye is removed to create an opening that allows aqueous humour to drain from the eye) [1]. Trabeculectomy with antimetabolite therapy is the treatment of choice for patients suffering from ARS.

The aim of conservative dental rehabilitation is twofold, to improve both aesthetics and function. In the long term, dental implants remain the most likely treatment option for these patients. Close liaison between dental professionals is essential to monitor facial growth and dental development, and to coordinate appropriate timing for dental treatment.

What this case report adds

- A 10-year old girl with Axenfeld-Riger syndrome presented with a retained primary dentition demonstrating gross attrition.
- In total 15 permanent teeth were absent (including third molars).
- This severe hypodontia with missing central and lateral incisors and second premolars is characteristic of the syndrome.

Why this case report is important to paediatric dentists

- Early diagnosis of the Axenfeld-Riger syndrome from its dento-facial features is important since subsequent ocular complications may be prevented.
- Children with this syndrome exhibit a wide range of craniofacial and dental disturbances such as maxillary and mandibular hypoplasia, hypodontia, enamel hypoplasia and microdontia.
- The aim of dental rehabilitation is to improve both aesthetics and function. Dental implants is the most likely treatment option for these patients.

Conclusion

In clinical practice, it is necessary to differentiate *de novo* hypodontia from that which is syndrome-related. This involves close interdisciplinary management between dentists, paediatricians and geneticists.

Early diagnosis of the dental, cranio-facial and systemic presentation of ARS could prevent the devastating ocular effects of infantile glaucoma.

Acknowledgements

The authors wish to thank Dr J. Cooper, Specialist Registrar in Orthodontics at Arrowe Park Hospital, for his clinical photographs.

Résumé. Le syndrome de Axenfeld-Rieger (ARS) est une maladie autosomique dominante rare. Elle comprend des éléments des syndromes de Axenfelds et Riegers, indiquant que ces deux maladies sont des expressions variables d'une même anomalie de gène. Le syndrome est caractérisé par un développement arrêté ou perturbé des cellules de la crête neurale dans la chambre antérieure de l'œil, les os de la face, les dents, l peau péri-ombilicale et le système cardiovasculaire. Un diagnostic précoce de ce syndrome à partir des caractéristiques dento-faciales et systémiques est important car les complications oculaires subséquentes peuvent être prévenues. Le cas d'une jeune fille de 10 ans est décrit.

Zusammenfassung. Axenfeld-Rieger Syndrom (ARS) ist eine seltenen Erkrankung mit autosomal dominanter Vererbung. Diese beeinhaltet Symptome von Axenfeld Syndrom und Rieger Syndrom, was darauf hindeutet, dass beide Krankheitsbilder auf Veränderungen des gleichen Gens zurückzuführen sind. Charakteristisch für dieses Syndrom ist veränderte oder unterbliebene Entwicklung von Zellen aus der Neuralrinne mit Auswirkungen auf Auge, Gesichtsknochen, Zähne, periumbilikale Haut und das kardiovaskuläre System. Die frühzeitige Diagnose anhand der dentofazialen und systemischen Symptome ist wichtig, da dann Komplikationen am Auge verhindert werden können. Der Fall einer 10 jährigen Patientin wird vorgestellt.

Resumen. El síndrome de Axenfeld-Riegers (SAR) es una rara alteración autosómica dominante. Incorpora rasgos de los síndromes de Axenfelds y Riegers e indica que ambas alteraciones son expresiones variables de la misma anormalidad genética. El síndrome se caracteriza por desarrollo retrasado o detenido de las células de la cresta neural en la cámara anterior del ojo, huesos faciales, dientes, piel periumbilical y sistema cardiovascular. Es importante el diagnóstico precoz del síndrome por sus rasgos dento-faciales y sistémicos para que puedan prevenirse las complicaciones oculares posteriores. Se describe la presentación de un caso en una niña de 10 años.

References

1 Shields MB, Buckley E, Klintworth GK, Thresher R. Axenfeld–Rieger syndrome. A spectrum of developmental disorders. *Survey of Ophthalmology* 1985; **29**: 387.
2 Wesley RK, Golnick AL. Rieger's Syndrome. *Journal of Pediatric Ophthalmology and Strabismus* 1978; **15** (2): 67–70.
3 Tabbara KF, Khouri FP, Der Kaloustian V. Rieger's Syndrome with chromosomal anomaly. *Canadian Journal of Ophthalmology* 1973; **8**: 488–490.
4 Gorlin R, Pindborg J, Cohen M. Rieger's syndrome. In: Gorlin R, Pindborg J, Cohen M. (eds). *Syndromes of the Head and Neck*, 2nd edn. New York, NY: McGraw-Hill, 1976: 649–651.
5 Riekman G. Rieger's syndrome: case report. *Canadian Journal of Dentistry for Children* 1981; **48** (1): 55–56.
6 Grosso S, Farnetani MA, Berardi R, *et al*. Familial Axenfeld–Rieger Anomaly, cardiac malformations and sensorineural hearing loss: a provisionally unique genetic syndrome? *American Journal of Medical Genetics* 2002; **111**: 182–186.
7 Jorgenson RJ, Stefan Levin L, Cross HE, Yoder F, Kelly TE. The Rieger Syndrome. *American Journal of Medical Genetics* 1978; **2**: 307–318.
8 Fitch N, Kabach M. The Axenfeld Syndrome and the Rieger Syndrome. *The Journal of Medical Genetics* 1978; **15**: 30–34.
9 Lapeer G. Rieger's Syndrome, severe dental anomalies with mild ophthalmic changes – a case report. *Journal of the Canadian Dental Association* 1986; **11**: 935–937.
10 Dimitrakopoulos J, Voyatzis N, Katopodi T. Rieger syndrome: a case report. *Journal of Oral and Maxillofacial Surgery* 1997; **55**: 517–521.
11 Heckenlively JR, Istenburg SJ, Fox LE. The Rieger Syndrome: a heritable disorder associated with glaucoma. *The Johns Hopkins Medical Journal* 1982; **151** (6): 351–355.
12 Childers NK, Wright JT. Dental and craniofacial anomalies of Axenfeld–Rieger syndrome. *Journal of Oral Pathology* 1986; **15**: 534–539.
13 Prabhu NT, John R, Munshi AK. Rieger's syndrome: a case report. *Quintessence International* 1997; **28**: 749–752.
14 Scarparo Caldo-Teixera A, Puppin-Rontani RM. Management of severe partial hypodontia: case report. *Journal of Clinical Pediatric Dentistry* 2003; **27** (2): 133–136.
15 Ozekis H, Shirai S, Ikeda K, Ogura Y. Anomalies associated with Axenfeld–Rieger syndrome. *Graese's Archive for Clinical and Experimental Ophthalmology* 1999; **237** (9): 730–734.
16 Vaux C, Sheffield L, Gregory Keith C, Voullaire L. Evidence that Rieger syndrome maps to 4q25 or 4q27. *Journal of Medical Genetics* 1992; **29**: 256–258.
17 Priston M, Kozlowski K, Gill D, *et al*. Functional analyses of two newly identified PITX2 mutants reveal a novel molecular mechanism for Axenfeld–Rieger syndrome. *Human Molecular Genetics* 2001; **10** (16): 1631–1638.
18 Epinoza HM, Cox CJ, Semina EV, Amendit BA. A molecular basis for differential developmental deformities in Axenfeld–Rieger's syndrome. *Human Molecular Genetics* 2002; **11** (7): 743–753.