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Artículo Original

Otologic and Audiologic Findings in Children with Fanconi Anemia

Alterações Otológicas e Audiológicas em crianças com Anemia de Fanconi

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Abstract

Introduction: There is a paucity of research on otologic and audiologic abnormalities in Fanconi Anemia (FA). Since these alterations are not entirely characterized the main aim of this study is to describe the otologic and audiologic alterations in children with FA referred to our pediatric hearing loss consultation as part of the clinical evaluation protocol established.

Methods: The medical records of eleven patients were reviewed and patient demographics, clinical features associated with FA and otologic and audiologic findings were analyzed.

Results: Eleven patients, aged between one month and eight years old at diagnosis, were analyzed. Seven out of the eleven cases had hearing loss.

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Typically it was an asymmetrical conductive hearing loss, primarily affecting the lower frequencies. Three patients presented with unilateral external ear anomalies. In two cases the hearing loss was progressive.

Conclusions: The otologic and audiologic abnormalities in FA patients are not universal but were present in a considerable number of patients in our study. It is important for children with FA to be routinely submitted to an audiologic and otolaryngologist evaluation to promote early diagnosis and intervention.

Keywords: Fanconi anemia, Otology, Conductive hearing loss, Ear anomalies

Resumo

Introdução: Verifica-se uma escassez de estudos no que diz respeito às alterações otológicas e audiológicas da Anemia de Fanconi (AF). Uma vez que estas alterações não estão inteiramente caracterizadas, o principal objetivo deste estudo é descrever as alterações otológicas e audiológicas em crianças com AF que foram referenciadas à nossa consulta de surdez infantil, como parte do protocolo de avaliação clínica estabelecida.

Material e Métodos: Procedeu-se à revisão dos processos clínicos de onze doentes que cumpriram os critérios de inclusão. Foram recolhidos os dados demográficos do paciente, as características clínicas associadas a FA e foram analisados os achados otológicos e audiológicos.

Resultados: Onze doentes, com idades entre um mês e oito anos de idade no momento do diagnóstico, foram analisados. Sete dos onze casos apresentaram hipoacusia. Na maioria tratava-se era uma hipoacusia de condução assimétrica, afetando principalmente as frequências mais baixas. Três doentes apresentavam malformações unilaterais do ouvido externo. Em dois casos, a hipoacusia foi progressiva.

Conclusões: As alterações otológicas e audiológicas em doentes com AF não são universais, mas estavam presentes em um número considerável de doentes no nosso estudo. É importante que as crianças com AF sejam rotineiramente submetidos à avaliação audiológica e por um otorrinolaringologista de forma a promover o diagnóstico e intervenção precoces.

Palavras chave: Anemia de Fanconi, Otologia, Hipoacusia de condução, Malformações do ouvido

Introduction

Fanconi anemia (FA) is an autosomal recessive or X-linked condition first described in 1927 by Guido Fanconi. The incidence of FA is approximately 3/1 000 000 and the heterozygote frequency is estimated in 1/300. FA has been reported in many ethnic groups and founder mutations have been described in Ashkenazi Jews and Afrikaners^{1, 2, 3}.

On a cellular level, FA is characterized by chromosomal hypersensitivity to cross-linking agents that results in a high degree of genomic instability, especially on exposure to alkylating agents. So far mutations in at least 15 DNA repair genes (FANC genes) have been identified, the most frequent being FANCA, FANCC, FANCG and FANCD2^{4,5}.

Clinically, FA is a very heterogeneous condition and patients may present with a wide variety of abnormalities. There are typically several clinical stages in FA that are related to age². Homozygotes can present at birth with physical congenital abnormalities or during childhood with hematopoietic abnormalities. Hematologic anomalies are the most important clinical features of FA. In fact, FA is the most common type of inherited bone marrow failure syndrome. Pancytopenia typically presents between the ages of 5 and 10 years. Other clinical features of FA include skeletal abnormalities (thumbs and radial hypoplasia, congenital hip dislocation, scoliosis and other vertebral anomalies – 70%), altered skin pigmentation (*café-au-lait* spots, areas of hypo- or hyperpigmentation – 60%), short stature (60%), renal anomalies (unilateral renal aplasia, renal hypoplasia, horseshoe kidneys or double ureters – 30%), microcephaly (25%), microphtalmia (20%), genital abnormalities (hypogonitalia, undescended testes and hypospadias – 20%), developmental delay (10%) and hearing anomalies (external ear malformations and hearing loss – 10%)^{1,2,3}.

The main causes of morbidity and mortality are aplastic anemia, myelodisplasia, acute myeloid leukemia and, later, solid tumors in those surviving the childhood hematologic malignancies (hepatic tumors and squamous cell carcinomas of the head and neck region)^{1,2,3}.

In fact, in FA patients head and neck squamous cell carcinomas are the most frequently diagnosed solid tumors⁶. This fact combined with the uttermost importance of early surgical interventions emphasizes the need for regular and rigorous surveillance, ideally performed by an otolaryngology specialist^{6,7,8}.

Therefore, the management of this condition includes, when possible, improvement of physical anomalies, medical treatment of hematological complications and malignancy surveillance.

Otologic and audiologic alterations in FA include congenital anomalies of the external and/or middle ear and hearing loss that has been described as conductive, asymmetrical and may be progressive^{9,10,11}.

There is a paucity of research on otologic and audiologic abnormalities in FA. There are only a few case reports describing the ear manifestations of this condition in literature. Since these alterations are not entirely characterized the main aim of this study is to describe the otologic and audiologic alterations in children with FA attending the pediatric hearing loss consultation in our hospital.

Material and Methods

Children with FA are referred to the pediatric hearing loss consultation as part of the multidisciplinary clinical protocol established in our hospital, which includes evaluation by pediatrics, otolaryngology, hematology and genetics. According to what is defined in this protocol children with the diagnosis of FA should be referred for an otolaryngologist consultation in order to evaluate de presence of morphologic anomalies, to perform an audiologic evaluation and, if the child is over 10 years old, to screen for head

and neck squamous cell carcinomas. After that these children should perform an audiologic evaluation and screen for head and neck squamous cell carcinoma annually. Children over 15 years old or under treatment with ototoxic drugs should be evaluated by an otolaryngologist every six months.

Medical records of eleven patients with FA were reviewed. Data collected included patient demographics, clinical abnormalities at diagnosis, the otolaryngologist clinical evaluation and the results of pure tone audiometry and tympanometry. The average audiometric thresholds were determined by calculating the mean of the values obtained in the 250, 500, 1000, 2000 and 4000 Hz frequencies in each ear of the most recent exam performed.

Results

Eleven patients (7 females and 4 males) aged between 1 month and 8 years old at diagnosis, were analysed (Table 1). All had a minimum period of follow-up of 1 year, with a maximum 10 year follow-up period. The mean age at diagnosis was 3.9 years. Two children were diagnosed in early infancy during the screening of relatives since they are siblings of FA patients. The mean age at first otolaryngology consultation was 4.5 years. It is noteworthy that patient number 3 was referred to our consultation prior to FA diagnosis since he failed to pass the newborn universal hearing screening program.

All patients had hematologic abnormalities associated (macrocytosis and thrombocytopenia were the most common at diagnosis). Other clinical findings were present, the most frequent being skeletal abnormalities and abnormal skin pigmentation (*café-au-lait* spots).

When referring to abnormalities on the otolaryngology clinical examination 3 patients (27%) presented with asymmetrical external ear anomalies (type I microtia and stenosis of the ear canal).

Overall 7 out of the 11 cases had hearing loss (64%). Typically it was an asymmetrical conductive hearing loss, primarily affecting the lower frequencies that varied between 35 and 68 dB HL in the worst ear (figure 1). In 2 of these cases (18%) the hearing loss was progressive (figure 2 and 3). It was unilateral in 2 cases.

Tympanometry was performed in all patients. We obtained a type A in 4 patients, type As in 5 patients and the other 3 presented with a type B tympanogram.

In terms of hearing rehabilitation, patient number 10 was fitted with a bone-conduction hearing aid softband and patient 9 has a hearing aid (initially she was implanted with a bone-anchored hearing aid but due to frequent local infections it was decided to remove it).

Table 1: Clinical features of children with FA.

Patient	Gender	Age at diagnosis	Age at first ORL evaluation	Follow-up (years)	Clinical Abnormalities	Otologic Findings	Audiometric Findings	Degree of hearing loss (dB HL)	Tympanogram
1	M	21 mo	3 yo	7	Haematological abnormalities, skeletal abnormalities, Cardiac anomalies, Café-au-lait spots, Hypospadias	None	Unilateral conductive hearing loss	RE – 35 LE - 10	As
2	M	1 mo	12 mo	10	Renal anomalies, Cardiac anomalies, Café-au-lait spots	None	Normal thresholds	-	A
3	M	2 yo	12 mo	3	Haematological abnormalities, Cardiac anomalies, Renal anomalies, Hypospadias, Short stature	None	Bilateral asymmetrical conductive hearing loss	RE – 40 LE - 30	As
4	M	3 yo	3 yo	2	Haematological abnormalities, Short stature, Café-au-lait spots, Microcephaly	Bilateral external auditory canal stenosis Bilateral type I microtia	Bilateral asymmetrical conductive hearing loss	RE – 45 LE – 23	B
5	F	4 yo	4 yo	3	Haematological abnormalities, skeletal abnormalities, café-au-lait spots	None	Bilateral asymmetrical conductive hearing loss	RE – 25 LE – 30	B
6	F	4 yo	6 yo	7	Haematological abnormalities, Microphthalmia, Café-au-lait spots, skeletal abnormalities	None	Bilateral asymmetrical conductive hearing loss	RE – 60 LE – 20	As
7	F	4 yo	5 yo	9	Haematological abnormalities, Microcephaly, café-au-lait spots, skeletal abnormalities	None	Normal thresholds	-	A
8	F	4 yo	4 yo	2	Haematological abnormalities, café-au-lait spots	None	Normal thresholds	-	A
9	F	8 yo	9 yo	9	Haematological abnormalities, skeletal abnormalities, short stature, cardiac anomalies	Unilateral external auditory canal stenosis Unilateral type I microtia	Unilateral conductive hearing loss	RE – 20 LE – 60	As
10	F	8 yo	9 yo	10	Haematological abnormalities, skeletal abnormalities, short stature	Bilateral external auditory canal stenosis Bilateral type I microtia	Bilateral asymmetrical conductive hearing loss	RE – 47 LE – 68	RE – As LE – B
11	F	4 yo	3 yo	1	Haematological abnormalities, skin hyperpigmentation	None	Normal thresholds	-	A

yo – years old, mo – months old, RE – right ear, LE – left ear

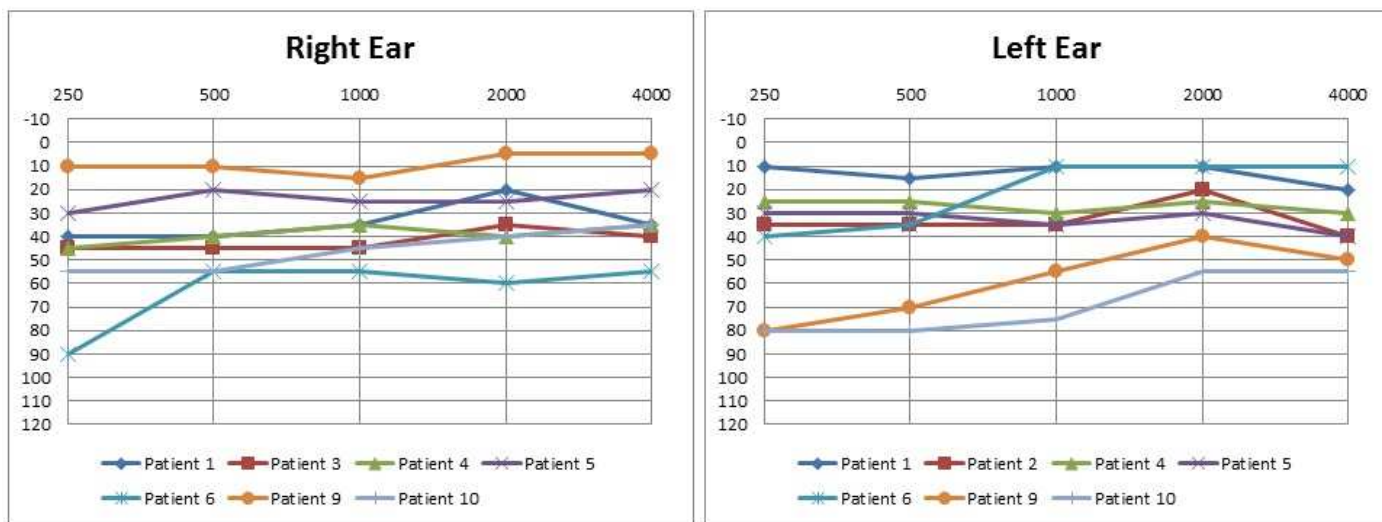


Figure 1 – Air thresholds for the seven patients with conductive hearing loss.

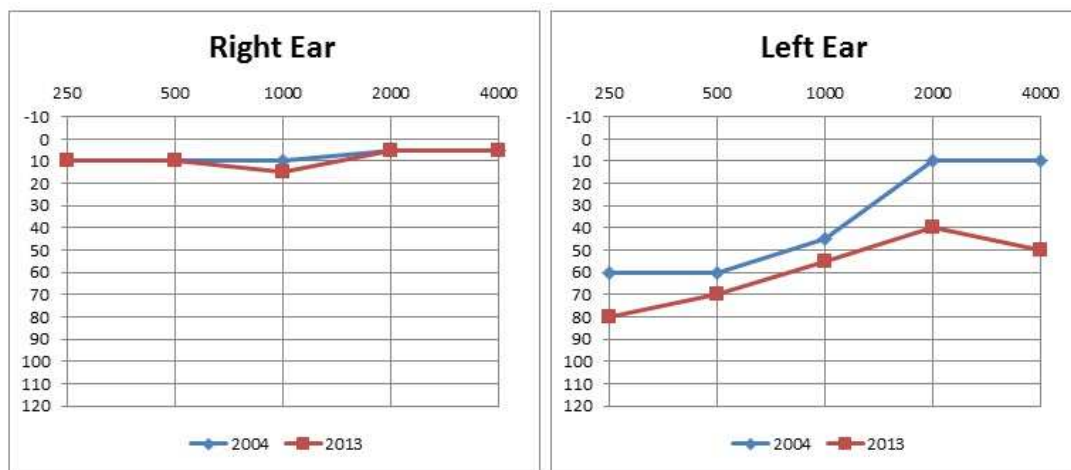


Figure 2 – Progressive conductive hearing loss in patient 9.

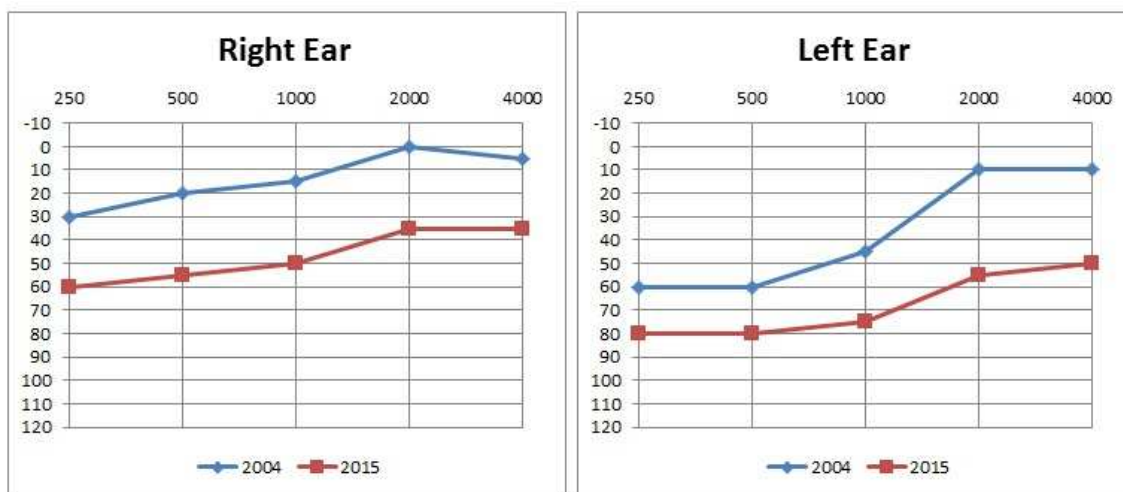


Figure 3 – Progressive conductive hearing loss in patient 10.

Discussion

There are few reports on otologic and audiological abnormalities in children with FA, although hearing loss and external ear malformations have already been reported as part of this disorder.

In our hospital all children with the diagnosis of FA are referred to an otolaryngology consultation as part of a multidisciplinary protocol established, regardless of the presence of otolaryngologic symptoms.

In our study hearing loss was present in 64% (n=7) of patients as an asymmetrical conductive type. In 27% of the patients (n=3) external ear malformations were identified. In repeated audiological evaluations we found a progression in hearing loss in 18% of the cases (n=2). We also found an asymmetrical conductive hearing loss and the ascending audiogram shape in all patients (Figure 1).

The results of our study complement and corroborate those of Vale *et al*¹¹, in terms of percentage of children with hearing loss (50%) and the audiogram pattern found. Also, a prospective study⁹ that analyzed 16 patients with FA reported hearing loss in 53% of them and the majority had a mild conductive hearing loss (65%). Santos *et al*⁶ reviewed 69 patients with FA diagnosis in all age groups and reported a lower percentage of FA patients with hearing loss (17.4%). Also they did not find a consistent audiogram pattern associated with this condition. It is noteworthy that of the 69 patients only 26 had audiograms. Nevertheless in that study all the patients with hearing loss had a conductive type. Likewise in Dokal study¹ 11% of the patients had a conductive hearing loss.

The most recent report regarding this subject, from Kalejaiye and colleagues¹², also concluded that FA is the major inherited bone marrow failure syndrome with associated hearing loss. In their series hearing loss was present in 45% of the patients with FA and was conductive in most cases (65%). Their results also showed that absent or hypoplastic radius was noted in 21% of the patients with FA and was associated with hearing loss in all cases. In our series 5 out of the 7 patients with hearing loss also presented with skeletal abnormalities (71%) but their varied from malformations of the thumbs to scoliosis and we didn't find such a strong association with radius malformations.

It is noteworthy that in our series there was a relatively high prevalence of altered tympanograms (type B in 27% and type As in 45%). This is also referred in Santos study¹⁰ (36%). This could suggest that FA patients are more susceptible to Eustachian tube dysfunction (possibly related to craniofacial dysmorfias) and that otitis media with effusion may have a higher prevalence in this group which. On the other hand, this may mask the presence of a conductive hearing loss related to other causes.

Also, as stated by Kim *et al* and Santos *et al*^{9, 10} the hearing loss in FA patients is more likely secondary to abnormalities in embryogenesis of the eardrum and/or ossicles, with some degree of ossicular fixation, resulting in a conductive hearing loss and a type B or a type As tympanogram. If it was secondary to the onset of hematologic anomalies it would suggest a vasculopathic mechanism and cause a sensorineural hearing loss.

In terms of external ear malformations our results (27%) are in line with those reported in literature. These reports are consistent and range from 12% to 32%^{10, 11, 12}.

The identification of Eustachian tube dysfunction and external ear malformations may suggest the presence of more subtle structural developmental anomalies affecting the temporal bone and related skull base.

None of our patients was evaluated with imaging studies (including Computer Tomography of the ear) since it is strongly recommended by the Pediatric Hematology Department to avoid exposure to radiations due to their high susceptibility to malignancy, specially head and neck carcinomas.

The results presented here should be interpreted considering the small sample size. Nevertheless they are consistent with other series and are important in reinforcing the need for awareness to the possibility of FA children present with otologic alterations or hearing impairment even before hematologic manifestations occur.

The otologic and audiologic abnormalities in FA patients are not universal but were present in a considerable number of patients in our study. This underscores the importance for children diagnosed with this condition to be routinely submitted to a comprehensive audiologic and otolaryngologic evaluation to promote early diagnosis and intervention.

Considering this disorder characteristics, success in management of patients with FA relies on a multidisciplinary and coordinated approach.

Conclusion

The otologic and audiologic abnormalities in FA patients are not universal but were present in a considerable number of patients in our study. It is important for children with FA to be routinely submitted to an audiologic and otolaryngologist evaluation to promote early diagnosis and intervention.

Conflicts of Interest

None

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