Case Report

Johnson-McMillin Microtia Syndrome: New Additional Family

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Abstract

Microtia is a congenital anomaly that is found with different prevalence among various populations. The exact etiology of ear anomalies is still unknown. We describe a new additional family with this rare disorder; Johnson–McMillin syndrome (JMS) where mother, son, and distant grandmother have multiple features of JMS in the form of microtia, facial asymmetry, ear malformation, hearing defect, and hypotrichosis. Variable presentations in this family could be referred to phenotype variation supporting an autosomal dominant pattern of inheritance. We observed that the mother was very sad and suffered from feelings of guilt. We found that she had isolated herself from family and community out of fear of being stigmatized and hurt. We concluded that the occurrence of microtia is of public health importance, adhering to traditional marriage customs in Egypt increases women's risk of giving birth to a disabled child, yet the mothers are blamed and shamed for their children's birth defects by their husbands, families, and communities, while the fathers are not stigmatized.

Keywords: Congential anomalies, Johnson–McMillin syndrome, microtia, neuroectodermal

Introduction

Microtia (OMIM 600674, OMIM 251800) is a congenital malformation, which occurs in around 1/8000-10,000 births,[1] with a prevalence that varies in different populations: Being 1.5/10,000 births in Italy,[2] 2.2/10,000 in California USA,[3] and 4.3/10,000 births in Finland, with an overall general incidence in other populations from 0.83 to 17.4/10,000.[4]

Microtia affects the size, shape and position of the ear and in some cases preauricular tags or pits are present. Various grades of microtia exist which range from the presence of all the features of normal auricle in Grade I to Grade IV in which there is no external ear and auditory canal, the detailed description of grades has been described previously.[5]

Several microtia syndrome have been described, Johnson-McMillin syndrome (JMS) is a rare neuroectodermal disorder that was first described in 1983 by Johnson *et al.*[6] The characteristic features include alopecia, ear malformations, conductive hearing loss, anosmia/hyposmia, and hypogonadotropic hypogonadism. Variable manifestations include mild facial asymmetry, mental retardation, congenital heart defect, and cleft palate. It is inherited in an autosomal dominant (AD) manner; however, the causative gene has not yet been identified.[7,8]

In 1983, Johnson *et al.* described 16 related individuals with a striking syndrome of alopecia, anosmia or hyposmia, conductive hearing loss, microtia and/or atresia of the external auditory canal, and hypogonadotrophic hypogonadism inherited in an AD pattern and with markedly variable expressivity.[6]

Variable manifestations included facial asymmetry, mental retardation, congenital heart defect, cleft palate, and canal atresia. A subsequent single case was reported.[9]

Case Report

Here, we describe a family that was referred to the Clinic of Special Needs, Medical Division, National Research Center, Cairo, with three family members showing signs of JMS.

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The presenting case is a 5-year-old male patient presenting with unilateral left sided microtia and left conductive hearing impairment.

He is the consequence of first-cousin's marriage. His mother was 21 years and his father was 28 years at birth of the child. No pregnancy problems were encountered and he was born at 39 weeks by normal vaginal delivery. Pregnancy and delivery history were irrelevant. His birth weight was 2.5 kg (9th centile), length was 48 cm (9th centile) and head circumference was 33 cm (9th centile).

On examination

Our index case, 5-year-old son has unilateral left sided Grade III microtia (with peanut-shell rudiment of soft tissue) with a total ear size 1.9 cm, atresia of auditory canal [Figure 1], and high arched palate. Left severe conductive deafness, and delayed language development were revealed, with multiple phonological errors. The left ear appears at lower level than the right ear, with broadened nasal root and bridge. Hyperpigmented cafe-au-lait patch on back, and left sided partial facial asymmetry with diminished muscle tone were evident.

Facial asymmetry was noted with narrow left palpebral fissure, diminished cheek, and chin prominence on left side. He had mild to moderate asymmetry in motor power, cranial nerves mainly the facial nerve, with intact symmetrical sensation. Hypotrichosis was seen with absent eyelashes, although he has normal eyebrows and no alopecia was noticed. Anosmia or hyposomia was not noticed in our case.

During the 1st year of life, he showed some delay in passive as well as active posture skills. Other skills that manifested with severe delay include hearing function, comprehension of language speech, and language skills. Interactive social skills and self-care social skills were also delayed.

Limbs and heart examination did not show any abnormalities. Genital examination at age of 5 years showed normal penile and testicular size with normal urethral meatus and normal anus.

Examination of skin showed one cafe-au-lait spot (3 × 3 cm in largest diameter) with serrated edges [Figure 2], with no other skin marks. Nose showed normal external orifices and no signs of choanal atresia and his palate is high arched, but did not affect feeding at any age.

Computed tomography scan of brain showed normal brain structures with atresia of left auditory canal. Auditory evoked response testing showed a severe conductive hearing loss in left side with normal sensorineural thresholds in both ears. Karyotyping showed normal chromosomes for the son and his mother.

Examination of the mother showed right sided unilateral malformed ear which is low set, with hypoplasia of the external auditory canal, conductive deafness, and right sided facial weakness and hypotrichosis [Figure 3]. She had history of transitional Alopecia, which gradually improved over several years. Grandparents were first-cousins [Figure 4]. Distant grandfather had two sisters; one of them had a history of unilateral microtia with conductive hearing loss and hypotrichosis (this history is given by the mother).

Discussion

The embryological defect in microtia with variable degrees are thought to be related to cell death of the first and second branchial arch derivatives, with numerous factors, e.g. race and gender being associative factors. The ectoderm and neuroectoderm of the first and second branchial arches are the main constituents of the manifestations of JMS. They give rise to auricles, ossicles, trigeminal and facial nerves. Neural crest involvement is also suspected since it gives rise to the endocardial

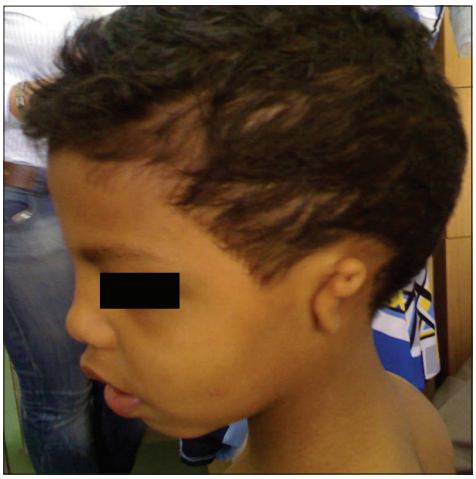

Figure 1: The 5-year-old son has left sided microtia and atresia of left auditory canal

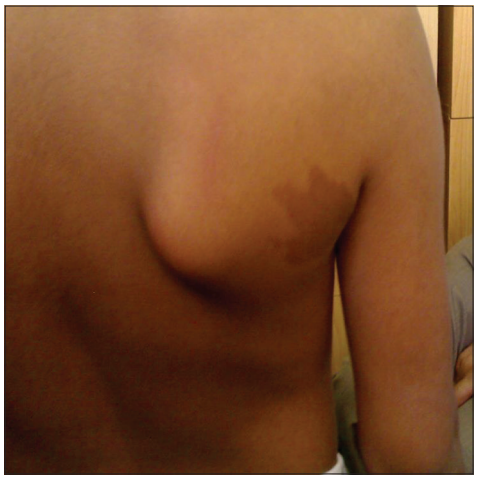

Figure 2: An irregular serrated café-au-lait patch on the back of our 5-year-old case

cushion and the truncus arteriousus of the embryological heart. Because the phenotypic abnormalities in JMS affect the brain, facial structures, ectoderm and its derivatives, outflow tract of the heart, and Rathke's pouch derivatives, this has suggested, Rathke's pouch, and the diencephalon contribution as well.[10]

Microtia is a clinical finding in several well-established human single gene disorders. Reviewing the literature showed that Mendelian inheritance is more likely in syndromic and familial cases of microtia, whereas multifactorial causes are more probable in sporadic cases.[11] Here, we describe a new family having JMS, with features of AD inheritance (with variable penetrance). Fear of stigmatization had influenced the mothers' treatment-seeking behavior for herself and for her child.

Pleiotropy with variable features of the syndrome was evident in affected family members. It was previously reported that AD inheritance pattern was the mostly reported mode of inheritance for JMS, although variable penetrance was obvious.[6,12]

The main features of JMS from the previous studies are summarized in Table 1, with various numbers of cases from different studies. It appears that the most consistent features of JMS are hair abnormality (alopecia, hypotrichosis), conductive hearing loss, ear anomalies, facial asymmetry with mental and growth deficiency. Other variable features include choanal atresia, congenital heart defects, anosmia/hyposomia, and cafe-au-lait spots of the skin.

Additional reported features are eyelid coloboma, cleft palate, abnormal ears, alopecia, delayed eruption and crowded teeth.[8] Hennekam and Holtus reported a mother and son with similar features. The mother had facial nerve palsy, cafe-au-lait spots, and mild developmental delays, while her son had microtia, hyposmia, hearing loss, and hypotrichosis.[12]

On 2003, unrelated female patient with severe features of this syndrome, whose mother and maternal grandfather's family showing much milder features, was described by Schweitzer *et al.*[10]

Another female patient with hypogonadotropic hypogonadism associated with JMS was described in 2004.[13] Other additional features were described in single case including preauricular tags and abnormal eye lids by Cushman *et al.* in 2005.[7] Our present family members showed most of the features of previously described for JMS. In addition, there is a family history of early-onset alopecia in the maternal grandfather's relatives.

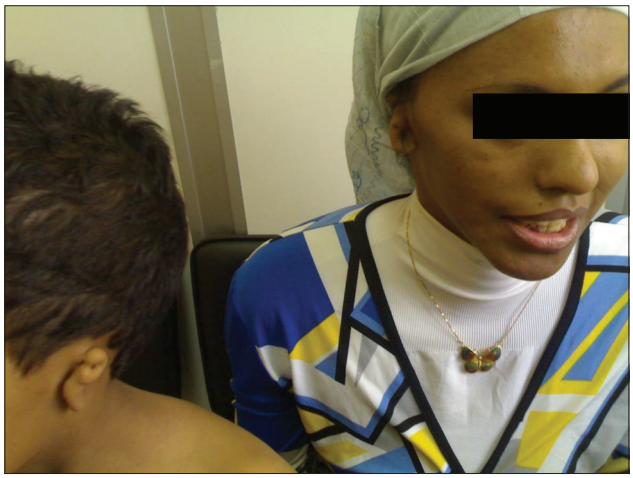

Figure 3: The Mother of the case with Johnson–McMillin syndrome (right- sided ear anomaly)

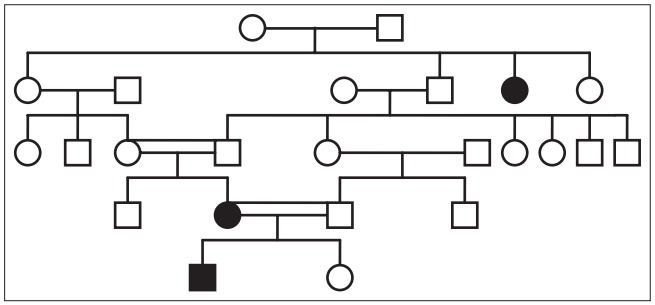

Figure 4: Pedigree of the family with three cases presenting with features of Johnson-McMillin syndrome (affected son, mother and distant grandmother)

Table 1: Features of JMS in previous studies with number of cases showing these findings

Clinical finding	Johnson *et al.* (1983) (16 case)	Johnston *et al.* (1987) (1 case)	Hennekam and Holtus (1993) (proposita and mother)	Schweitzer *et al.* (2003) (proposita and mother)	Cushman *et al.* (2005) (1 case)	Our family (3 cases)	Total number
Facial asymmetry	5/16	0/1	0/2	1/2	1/1	2/3	9/25
Alopecia	16/16	1/1	2/2	2/2	1/1	2/3	24/25
Ear abnormality	3/16	1/1	1/2	2/2	1/1	3/3	11/25
Conductive hearing loss	7/16	0/1	1/2	1/2	1/1	3/3	13/25
Cafe'-au-lait spots	0/16	1/1	2/2	0/2	?	1/3	3/25
Anosmia/hyposomia	3/16	0/1	1/2	1/2	0/1	0/3	5/25
Hypogonadism	3/16	0/1	0/2	1/2	0/1	0/3	4/25
Mental retardation	3/16	1/1	2/2	1/2	1/1	2/3	10/25
Growth deficiency	7/16	0/1	1/2	1/2	0/1	0/3	9/25
Choanal stenosis	1/16	0/1	0/2	2/2	0/1	0/3	3/25
Congenital heart defect	2/16	0/1	0/2	1/2	0/1	0/3	3/25

The mother of our index patient had mild features compared with her son; she has mild degree of deafness, mild language impairment, unilateral ear abnormality, and facial asymmetry. No skin cafe-au-lait spots or hyper pigmented areas are found. Distant grandmother showed ear abnormality and hypotrichosis, although a detailed history taking about her was difficult as she passed away.

Although the exact genes being involved in this syndrome is still unknown, many cellular factors were disturbed in gene expression studies of similar disorders, e.g. endothelin 1, dHAND, MSX1, which play a major role in craniofacial development *in-utero*.[14,15] Further studies are crucial to investigate the molecular defects and gene etiology of JMS.

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