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Congenital ocular motor apraxia

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Abstract

Aim: **To report the ocular and general features of a group of patients with congenital ocular motor apraxia (COMA).**
Methods: **Twenty-one patients with COMA who presented to the clinic, were seen following a review of the clinical database or were siblings of presenting cases are reported. All had a full paediatric, orthoptic and ophthalmic examination including video recording of head movements and determination of family incidence. Thirteen patients had a radiological examination.**
Results: **All patients showed the typical clinical features of COMA. In addition there was a variety of orthoptic, ophthalmic, paediatric and radiological findings. Half of the group had myopia, which ranged from –0.50 to –19 DS. There were 7 familial cases of COMA, which were associated with consanguineous marriage.**
Conclusion: **Patients with COMA may have a wide spectrum of ophthalmic and general abnormalities. The presence of familial cases within the group supports the theory of a genetic basis for some cases of COMA.**

Key words: Autosomal recessive, Congenital ocular motor apraxia (COMA), Consanguinity, Saccades

Introduction

Congenital ocular motor apraxia (COMA) is a rare disorder of unknown pathogenesis, which was first described by Cogan.[1] Subsequent reports of this condition have shown it to be sporadic, familial, most commonly congenital and rarely associated with neurodegenerative disorders.[2]

COMA usually presents in infancy as an apparent lack of visual attention and is usually reported by the parents in the belief that their child is blind. It is characterised by a failure to initiate horizontal saccades and in the majority of patients vertical movements remain intact. A jerky head-thrusting movement and an increased blink pattern are the main features of the condition. In order to move gaze horizontally from one object of fixation to another the affected individual utilises a horizontal head-thrusting movement, which in conjunction with the vestibulo-ocular reflex (VOR) allows the eyes to re-fixate on the horizontal plane. The head-thrusting movement is used to move the eyes to the object of fixation, after which the head is slowly returned to the straight-ahead position. Many patients show an increased blink pattern, which is used to break fixation so that re-fixation may be attempted. The head thrusts and increased blink pattern only occur when the child develops head control. Many affected children fail hearing tests as they are unable to generate horizontal saccades rapidly enough to fixate upon the auditory stimuli during testing.[3]

This paper reports on a group of patients with COMA and the variety of ocular and general abnormalities that may occur. Due to the familial incidence of COMA in this group it is proposed that in a proportion of cases COMA may be inherited as an autosomal recessive defect due to consanguinity, i.e. the intermarriage of blood relatives such as first-degree cousins.

Method

Twenty-one subjects were diagnosed as having COMA. There were 10 females and 11 males aged from 15 months to 16 years. All the participants were examined at the St John Ophthalmic Hospital in Jerusalem and Gaza between March 1998 and May 1999. Written consent was received prior to participation in the study.

The group comprised new patients and some recruited from the clinic's patient database. The use of the database was prompted by the apparently high presentation of new patients. Further new patients were recruited upon examination of siblings of affected individuals.

All subjects had a full paediatric, orthoptic and ophthalmic examination including refraction and fundus examination. CT scans were carried out on as many subjects as possible. The siblings and parents of the subjects were examined in order to detect any previously undiagnosed or improved cases. Video recordings were taken of the majority of the group, as well as of some of the normal siblings and parents. Examination of immediate family members and plotting of a family tree for at least two generations in all cases was undertaken to assist in the genetic investigation of this condition.

A detailed history was taken that included family history, medical and birth history, developmental history and a systematic enquiry of the history of the presenting signs. Orthoptic examination included visual acuity, cover test, ocular movements, assessment of binocular optokinetic nystagmus (OKN) and the presence of binocular single vision. Additional tests appropriate to each individual were also carried out where necessary.

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Results

The examination results of the group are shown in Table 1. There was a relatively high incidence of familial cases (patients 1–7). All subjects showed classic head-thrusting movements. This varied in severity according to the age of the child, appearing to lessen with age. Many, but not all, showed an increase in blink pattern but all children exhibited "locking-up" upon rotation or while viewing an optokinetic stimulus.

A wide variety of other ocular manifestations were documented. Ten children had manifest strabismus. One child had dissociated vertical divergence and 1 child had ptosis. Two children had bilateral developmental cataracts that had been removed and treated with aphakic spectacles. Fundal examinations revealed pale discs in 2 children and chorioretinal atrophy in 2 others. Retinitis pigmentosa was queried in 2 children.

Half of the group had myopia, which ranged from −0.50 to −19 DS. Four children had myopia of higher than −10.00 DS. Of the familial cases, 6 were myopic. This included a set of identical twins with myopic anisometropia (twin 1: R −11.50 DS L −3.50 DS; twin 2: R −3.50 DS L −0.50 DS). Their elder sister also had COMA and high myopic anisometropia (R −13.75 DS, L −19.00 DS).

The paediatric examination for 5 of the subjects was normal. Sixteen had abnormalities, which ranged in severity from delayed speech and walking, to moderate developmental delay associated with stunted growth and cleft palate, to severe mental retardation associated with poor hearing and poor speech. Four of the familial cases had slight development delay for starting to walk and/or talk.

Due to the political and financial restraints that exist in the Jerusalem and Gaza area, it was not possible to carry out CT scans on all the cases. Of the 13 subjects who were scanned only 4 revealed significant abnormalities. One child had a cerebral focal lesion although the ventricles were within normal limits, 2 children had brain atrophy and 1 child had agenesis of the corpus callosum and brain oedema. None of these children had a sibling in the study group.

Discussion

The size of the group described in this report appears to be relatively large compared with previous studies reporting COMA. The approximate population from which this group is drawn is 3.5 million. The complex political situation makes it very difficult for patients to be examined either in Jerusalem or in Gaza and it is likely that there are cases of COMA in this region that are undiagnosed. Consequently it is not possible to determine the prevalence of COMA in this area.

The 21 cases described exhibited the classic characteristics of COMA, which have been described by a variety of authors.[1,3,4] The lack of horizontal saccades was closely associated with abnormal head-thrusting, increased blink patterns and "locking-up" on extremes of gaze. Since children who exhibit COMA are unable to generate horizontal saccades, they are unable to perform the corrective saccade, which makes up part of the OKN response. Therefore, upon rotation, the eyes simply remain in the most extreme position of gaze of the direction opposite to that of rotation. Video footage clearly showed the head-thrusting movements and excessive blinking were greater in the younger children and were extremely hard to recognise in the teenage participants. This supports the theory that COMA appears to disappear or lessen with age.[6]

The paediatric examinations of the group revealed a wide variety of signs, many of which have previously been described as being associated with this condition,

Table 1. Characteristics of individual COMA patients including the results of the general, orthoptic and ophthalmological investigations

Patient no.	Sex	Squint	Head-thrusts	Excess blinks	Developmental delay	CT scan	Relationship of parents	Family history of COMA	Birth history	Refractive error
1	F	1	Present	Present	Yes	Normal	First cousin	Positive	FTND/ twin	Aniso-myope
2	F	1	Present	Present	Yes	Normal	First cousin	Positive	FTND/ twin	Aniso-myope
3	F	3	Present	Present	Yes	Normal	First cousin	Positive	FTND	High myope
4	F	2	Present	Present	No	Not done	First cousin	Positive	FTND	Aniso-myope
5	F	1	Present	Present	No	Normal	First cousin	Positive	FTND	Nil
6	F	3	Present	Present	Yes	Normal	First cousin	Positive	FTND	Aniso-myope
7	M	1	Present	Present	No	Normal	First cousin	Positive	FTND	Aniso-myope
8	F	1	Present	Present	No	Normal	First cousin	Negative	FTND	Nil
9	F	2	Present	Present	Yes	Normal	First cousin	Negative	FTND	Hypermetrope
10	M	4	Present	Absent	Yes	Not done	Second cousin	Negative	FTND	Myopic astig
11	M	1	Present	Present	Yes	Not done	Second cousin	Negative	FTND	Myopic astig
12	M	3	Present	Present	Yes	Abnormal	Second cousin	Negative	FT caesar	Aniso-myope
13	M	2	Present	Present	Yes	Not done	First cousin	Negative	FTND	Hypermetrope
14	F	3	Present	Absent	Yes	Abnormal	Not related	Negative	FTND	Hypermetrope
15	M	2	Present	Present	Yes	Abnormal	First cousin	Negative	FTND	Hypermetrope
16	M	1	Present	Present	Yes	Abnormal	Not related	Negative	7/52 prem	Nil
17	F	1	Present	Absent	No	Not done	Not related	Negative	FTND	Aphakic
18	M	1	Present	Present	Yes	Not done	Not related	Negative	FTND	Nil
19	M	2	Present	Present	Yes	Normal	Not related	Negative	FTND	High myope
20	M	1	Present	Present	Yes	Not done	First cousin	Negative	FT caesar	Hypermetrope
21	M	2	Present	Present	Yes	Not done	First cousin	Negative	FTND	Aphakic

Sex: M, male; F, female; *Squint:* 1, nil squint; 2, esotropia; 3, exotropia; 4, DVD; *Birth history:* FTND, full-term normal delivery; Caesar, caesarian section.

including agenesis of the corpus callosum, cleft palate, and developmental delay including delayed speech and late walking.[9] Other authors have also described associations with Gaucher's disease,[2] infantile hypotonia,[10], Joubert's syndrome,[11] Dandy Walker malformation,[12] hydrocephalus,[12] microcephaly[12] and cerebellar vermis hypoplasia.[13]

There were seven familial cases and these are summarised in Fig. 1. Family 1 consisted of a brother and sister; family 2 was two sisters; and family 3 identical twin sisters and a sister. All the familial cases were the product of consanguineous marriage, indicated by the double line linking the parents.

Consanguineous marriage is a very common social finding in the Palestinian population. Approximately 700 million people across the world practise consanguinity. In India alone 33% of Hindu families, 28% of Muslim families and 18.6% of Christian families practise it. Different cultures express different reasons for it. Some cultures believe that it will eliminate harmful genes from the population, but the majority of cultures practise it to keep the family wealth within the family and have the attitude "why marry a stranger?" However, the medical world is well aware that genetic disorders, which are coded by recessive genes and are usually not common in the general population, will occur more frequently in children who are the product of consanguineous marriage.

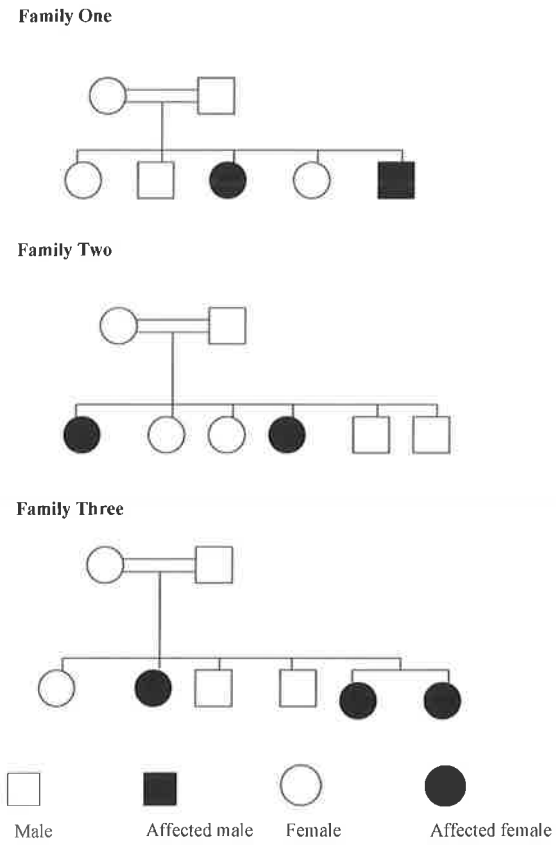

Fig. 1. The family trees of familial cases of COMA.

Autosomal recessive traits are only manifest when the allele is present in a double dose. Usually heterozygotes (carriers) are perfectly healthy as are the offspring of affected individuals. Unless a heterozygote marries a heterozygote, there is no possibility for the condition to become manifest.[14] Since the majority of recessive traits are very rare, this is very unlikely. However, since the intermarriage of first-degree relatives is a very common social finding within the Palestinian population, the likelihood of marrying someone who is also carrying a recessive gene for a rare disorder such as COMA is greatly increased. This could be a suitable explanation for the apparently high incidence of COMA in this population.

Many authors have attempted to pinpoint the genetic mapping of COMA. Yavuz Gürer *et al.*[4] suggested a probable genetic origin of COMA in some patients. They described cases in identical twins, father and daughter, and in association with X-linked muscle atrophies, but did not stipulate one specific mode of inheritance. Prasad and Nair[5] also felt that it was reasonable to assume a genetic origin for COMA. They reported on a family cluster of children in Saudi Arabia who exhibited COMA and commented that in that country marriages occur within closely knit communities. They postulated that an autosomal recessive pattern of inheritance could have been responsible for the involvement of three siblings of a large family. They suggested a prospective long-term study of succeeding generations would be necessary to reach a definitive conclusion.

Cogan[6] reported on familial cases and proposed that the reported number of familial cases he had reviewed was sufficient to indicate a genetic basis for a substantial proportion of cases of COMA. He emphasised the importance of examining all family members, in particular adults in whom the condition may have lessened such that it is not immediately recognisable. Cogan concluded that the familial incidence was most compatible with a recessive mode of inheritance and this belief was supported by the history of consanguineous marriage in one of the families.

Betz *et al.*[7] reported cases of children who carry deletions in the gene (NPHP1) for juvenile nephronophthisis and also exhibit COMA. Nephronophthisis type 1 is an autosomal recessive kidney disease, which leads to end-stage renal failure in adolescence. The occurrence of patients with nephronophthisis type 1 and COMA has previously been described.[8] By reporting further similar cases, Betz *et al.*[7] felt it was possible that there might be another gene present in the vicinity of the NPHP1 gene which gives rise to COMA. However, this would support the theory that COMA is inherited by an autosomal dominant mechanism, since an extended deletion would most likely be present only on one chromosome in a patient affected with COMA.

The increased incidence of COMA in the Palestinian population may be due to environmental, dietary or other factors that are specific only to this area. However, the presence of seven familial cases within this report implies a genetic basis for some cases of COMA. This is supported by the fact that all the familial cases were the product of marriages of first-degree cousins. All family members including siblings and parents were closely

examined to identify any previously undiagnosed cases. Special attention was paid to the teenage and adult participants, in whom COMA can be very difficult to recognise since it appears to lessen considerably with age.

Of the 7 familial cases, 6 had been scanned, all of which were normal. This may rule out brain insult or damage as being the aetiology and favour the hereditary cause. However, it is also possible that abnormalities are present which the CT scanning did not detect.

It is possible that the occurrence of COMA in identical twins (family 3) was due to a developmental abnormality. However, as their sister was also affected it seems more likely that the COMA in these particular twins had a genetic basis. In families 1 and 2 COMA was present in two siblings. Autosomal recessive conditions usually affect individuals in one sibship, i.e. affected individuals are brothers and sisters. Offspring of parents who are heterozygous for COMA have a 1 in 4 chance of being homozygous for that gene. This offers an explanation as to why not all of the siblings were affected.

Conclusion

In the Jerusalem and Gaza area COMA appeared to be a frequent clinical finding. The 21 patients reported exhibited the classic characteristics of COMA and in addition a variety of other ocular and general abnormalities. There was a high incidence of familial cases all of which occurred in just one sibship. This finding, combined with the association of consanguineous marriage, supports the theory that COMA, at least in a proportion of patients, may be inherited in an autosomal recessive fashion.

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