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Exploring the clinical profile and etiological spectrum of pediatric oculomotor apraxia: A retrospective analysis

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Abstract
Introduction: Oculomotor apraxia (OMA) is characterized by impaired voluntary eye movements, particularly in horizontal directions, while slow pursuit movements are retained. This study aims to investigate the clinical, laboratory, and neuroimaging features of OMA in pediatric patients, as well as its etiology, follow-up, and association with neurodevelopmental disorders.
Methods: A retrospective analysis was conducted between January 2013 and January 2023 in a Portuguese tertiary hospital.
Results: The sample comprised 19 patients, predominantly males (N=15; 78.9%), with onset age ranging from four months to 13 years-old (median= 23 months). Neurological changes were evident at referral, with additional alterations observed during follow-up, including ataxia and dysarthria. Analytical, metabolic, and genetic studies aided in diagnosing 12 patients, with six cases identified as idiopathic OMA. Among idiopathic OMA, familial history was present in two cases. During an average follow-up period, three patients with idiopathic OMA exhibited global developmental delay (GDD), and two had attention deficit hyperactivity disorder.
Discussion: The study highlights idiopathic OMA as a diagnosis of exclusion, often presenting with normal blood work and imaging studies. GDD is present in half of the cases, having been appropriately referenced. Familial associations, subtle MRI changes, and GDD suggest potential underlying genetic factors that warrant further investigation.

Keywords: Developmental disorders, oculomotor apraxia, Idiopathic oculomotor apraxia; Pediatric patients

Introduction
Oculomotor apraxia (OMA) was first described in 1952 by Professor David Cogan, who examined four children showing a distinct gaze disorder accompanied by compensatory head movements [1]. This condition involves difficulty in executing voluntary, horizontal, rapid eye movements while maintaining slow pursuit movements [2]. While OMA was originally mainly linked to deficiencies in horizontal gaze, it is now known to appear in a variety of ways in a wide range of neurological conditions [2-4]. OMA may be divided into three categories: idiopathic congenital, acquired, or associated with other conditions [5, 6].
Idiopathic congenital OMA, also known as "Cogan-type" or recently named infantile-onset saccade initiation delay (ISID), is characterized by the absence or impairment of voluntary horizontal saccadic movements [1-6]. While reflexive saccades such as the fast optokinetic response and vestibulo-ocular reflex remain intact [3], individuals with ISID often exhibit saccadic hypometria alongside normal saccadic velocity [2]. ISID is presumed to have a genetic basis; however, various patterns of inheritance have been observed without any identified gene [9-11]. Typically, ISID manifests in early infancy with jerky horizontal head movements or thrusts upon attempting lateral gaze, often accompanied by compensatory head movements [2, 4]. Diagnosis usually occurs within the first year of life (coinciding with the development of head control), although visual tracking difficulties may be noted around two months of age [3, 4]. As children with ISID grow, head thrusts may diminish and may be replaced by blinking, particularly evident in moments of fatigue or anxiety [12].

Additional features commonly associated with ISID include hypotonia, clumsiness, ataxia, global developmental delay (GDD) and behavior disorders. However, the prevalence of these features remains uncertain [2, 3]. Neuroradiological findings in ISID patients can range from normal to subtle structural abnormalities, frequently involving the cerebellar vermis, and occasionally affecting other brain regions such as the infratentorial area, cerebrum, corpus callosum, thalamus, and basal ganglia [4].

Acquired OMA is characterized by difficulty initiating saccades towards visual stimuli or commands in all directions [3]. This form of OMA can arise following bilateral lesions affecting regions such as the posterior cerebral hemisphere, frontal eye fields, or basal ganglia, and may also be associated with conditions like frontotemporal lobar degeneration, Huntington's disease, or corticobasal syndrome [3, 5, 8].

Furthermore, OMA may occur concomitantly with other neurological or developmental disorders, including structural defects (abnormalities in the corpus callosum, cerebellum or fourth ventricle), neurodegenerative diseases (ataxia with oculomotor apraxia types 1, 2, and 4 (AOA1, AOA2, AOA4), Ataxia-Telangiectasia), and metabolic disorders (Gaucher disease, Leigh syndrome, and Niemann-Pick type C) [5, 6, 7, 12].

Objectives

The aim of the study was to review the clinical, laboratory, genetic, and imaging characteristics of pediatric cases of OMA and their correlation with etiology, follow-up and neurodevelopmental disorders.

Methods

We conducted a retrospective analysis of the medical records of all children diagnosed with OMA in the Neuropediatrics unit at Centro Materno Infantil do Norte between January 2013 and January 2023. Oculomotor apraxia was characterized by increased saccadic latencies, head thrusts, and/or oculocephalic dissociation. Patients were identified from a database containing demographic information such as age, gender, age at onset, first symptoms, and family history. Each patient underwent a comprehensive clinical, ophthalmological, and detailed neurological examination. We described analytical and neuroimaging findings, development milestones, the multidisciplinary approach carried out, diagnosis, and treatment, if applicable.

Axial T_1, T_2, coronal fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI), and proton density were among the neuroimaging studies conducted. The investigation was conducted in accordance with each patient's clinical presentation. Commonly requested tests included alpha-fetoprotein (AFP), albumin, triglycerides, cholesterol levels, immunoglobulins, and lymphocyte subpopulations. When necessary, metabolic analysis encompassed assessments such as fatty acid profiles, isoelectric focusing of transferrin, beta-galactosidase, beta-chitotriosidase, lysosphingomyelin levels, and amino acid levels. Neuropathy was investigated using four-limb electromyography. Ophthalmological examination including visual acuity. Developmental and motor outcomes assessed included GDD, reading difficulties, behavioral difficulties and speech or language delay.

Results

The sample comprised 19 patients (see figure 1), with a male predominance (n=15; 78.9%). The age at onset of OMA ranged from four months to 13 years, with a median of 23 months; the interval to the first appointment ranged from four months to 12 years, with a median of 20 months. In the neurological examination, beyond OMA in 11 patients, nine had hypotonia and five had ataxia. During follow-up, additional neurological alterations were observed, including ataxia in 10 patients, OMA in eight, dysarthria in five, choreiform movements in two and, supranuclear paresis and axonal neuropathy in one patient. All patients had ophthalmological observations which showed: chorioretinal colobomas in two patients, and ocular/conjunctival telangiectasia in another two.

An in-depth etiological investigation customized for each patient's clinical presentation was conducted. Brain MRI revealed abnormalities in eight patients: six with cerebellar vermis hypoplasia (including five with the "molar tooth" sign), one with T_2 and T_2 FLAIR hyperintensity of the cerebral white matter (frontal and parietal periventricular), and one with Budd-Chiari I malformation. Genetic analysis included an array, ataxia panel, S. Joubert panel, and a panel associated with movement disorders and/or ciliopathies. Joubert syndrome was diagnosed in five patients (mutations in the TMEM67 gene and CC2D2A gene), ataxia-telangiectasia in three (mutation in the ATM gene), Niemann Pick type C in one (mutation in the NPC1 gene), AOA4 in two (mutation in the PNKP gene), and spinocerebellar ataxia 42 in another patient (mutation in the CACNA1G gene) (refer to Table 1).

After extensive investigation, idiopathic congenital OMA was diagnosed in six patients. One patient is still awaiting genetic study and was not included in these numbers.

In the group of idiopathic congenital OMA (N=6), familial history was positive in two patients: one in which the patient´s father had OMA as well as a cousin, and another had a cousin with OMA. In this group, onset age of OMA ranged from four months to 12 months, with a median of eight months; the interval to the first appointment ranged from four months to 20 months, with a median of nine months. Neurological examination at the time of referral showed hypotonia in four patients and OMA in another four patients. Throughout the follow-up period (median of seven years and nine months, with a minimum of 18 months and a maximum of 13.4 years), all patients' analytical, metabolic, and genetic investigations remained normal. MRI was abnormal in one patient, showing cerebellar vermis hypoplasia. Three patients had GDD, manifesting with language delay and learning difficulties, and two patients had attention deficit hyperactivity disorder (ADHD). These patients were referred to speech and occupational therapy and psychology and physical medicine and rehabilitation consultations (refer to Table 2).

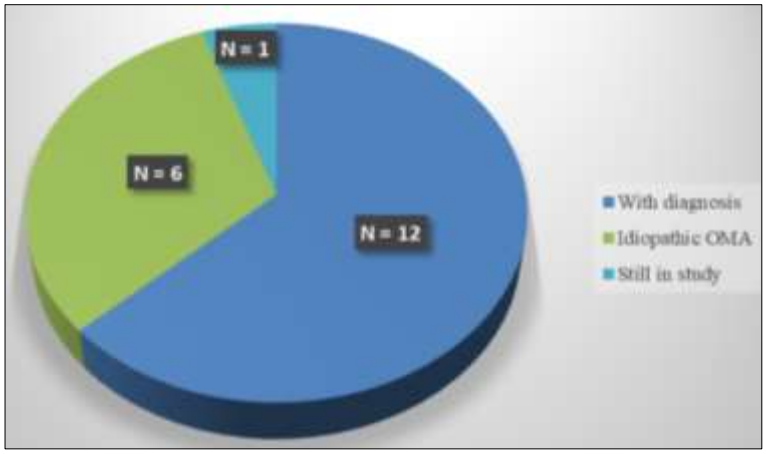

Fig 1: Distribution of Study Participants

Legend: N= number of patients; OMA: oculomotor apraxia

Note: Diagnoses included in "With diagnosis": Joubert syndrome, ataxia-telangiectasia, Niemann Pick type C, AOA4 and spinocerebellar ataxia 42.

Table 1: Characterization of the sample regarding the etiological investigation conducted and the final diagnosis.

Patients	Age of Onset of OMA	Gender	Neurological Findings*	Ophthalmological Examination	Analytical and Metabolic Study	Neuroimaging (MRI)	Genetic Study	Clinical Evolution	Diagnosis
1.	5 m	F	Axial hypotonia	Normal	Normal	Inferior vermian hypoplasia	Ataxia Panel: Normal	Ataxia	Idiopathic OMA
2.	5 m	M	Axial hypotonia	Optic disc dysplasia Chorioretinal colobomas	Normal	Vermian hypoplasia 'Molar tooth' signs	Joubert Panel: 3 Variants of Uncertain Significance in autosomal recessive gene	Ataxia OMA	Joubert syndrome
3.	10 m	F	OMA	Normal	Normal	Superior vermian hypoplasia 'Molar tooth' signs	Ataxia Panel: normal	Ataxia	Joubert syndrome
4.	11 m	M	OMA	Normal	Normal	Chiari malformation type I	Ataxia Panel and Panel associated with movement disorders: normal	Ataxia	Idiopathic OMA
5.	5 m	M	Hypotonia OMA	Normal	Normal	Normal	Panel associated with movement disorders: normal	OMA	Idiopathic OMA
6.	34 m	F	Ataxia	Chorioretinal colobomas	Normal	Vermian hypoplasia 'Molar tooth' signs	Panel associated with ciliopathies: variant c.1981_1982delinsTp(Ala661serfs*5) in TMEM67 gene	OMA	Joubert syndrome
7.	4 m	F	OMA	Normal	Normal	Normal	Array and ataxia panel: normal	OMA	Idiopathic OMA
8.	154 m	M	Ataxia Dystonia OMA	Normal	Elevated lysosphingomyelins	T2 and T2 FLAIR hyperintensity of the cerebral white matter	Ataxia panel: Compound heterozygosity of the genetic variants c.410C>T (p.T137M) and c.3104C>T (p.A1035V) in NPC1 gene	Supranuclear paresis	Niemann Pick type C
9.	12 m	M	Hypotonia	Normal	Normal	Normal	Array and ataxia panel: normal	OMA Ataxia Dysarthria	Idiopathic OMA
10.	143 m	M	OMA	Normal	Normal	Vermian hypoplasia 'Molar tooth' signs	Ataxia panel: heterozygosity two variants c.4583G>A (p.Arg1528His) and c.3904C>T (p.Arg130Cys) in CC2D2A gene	Ataxia	Joubert syndrome
11.	64 m	M	Ataxia OMA	Normal	Elevated pyruvate	Normal	Ataxia panel: heterozygosity in CACNA1G gene	Choreiform movements	Spinocerebellar ataxia 42
12.	9 m	M	Hypotonia	Normal	Hypogammaglob	Normal	Array: normal	Ataxia	Atelectasis –

					ulinemia and elevated alpha-fetoprotein		Molecular study: allele 1 - variant c.6677T>C (p.(Leuc2226Pro)) - exon 46; allele 2 - variant c.8292_8293del(p.(Ser2764Argfs*4)) - exon 57	Dysarthria OMA	telangiectasia
13.	158 m	M	Hypotonia OMA	Normal	Normal	Normal	Ataxia panel: compound heterozygosity in PNKP gene	Choreiform movements Dysarthria Axonal neuropathy	AOA4
14.	37 m	M	Ataxia	Normal	Normal	Normal	Ataxia panel: compound heterozygosity in PNKP gene	OMA	AOA4
15.	11 m	M	Hypotonia	Normal	Normal	Normal	Array and ataxia panel: normal	OMA	Idiopathic OMA
16.	49 m	M	Ataxia	Ocular telangiectasia	T and NK cell expansion	Normal	Ataxia panel: homozygous c.67C>T(p.Arg23*) in ATM gene	OMA Ataxia Dysarthria	Atelectasis – telangiectasia
17.	33 m	M	Hypotonia	Ocular telangiectasia	Normal	Normal	Ataxia panel: mutation in ATM gene	Ataxia OMA Dysarthria	Atelectasis – telangiectasia
18.	37 m	M	Hypotonia OMA	Normal	Normal	Normal	Ataxia panel: VUS in SAMD9L and VPS13D gene	Ataxia	Ongoing
19.	23 m	M	OMA	Normal	Normal	Vermian hypoplasia ‘Molar tooth’ signs	Ataxia panel: normal	Ataxia OMA	Joubert syndrome

Legends: *At the moment of referral; F – female; m – months; M – male; MRI – Magnetic Resonance Imaging; OMA – Oculomotor apraxia; VUS - Variant of uncertain significance

Table 2: Characterization of the idiopathic OMA in relation to the etiological investigation, follow-up time, developmental and referral

Patients	Age of OMA onset	Age at first appointment	Familiar history	Follow-up time	Neurological findings*	Developmental	Referral
1	5 m	5 m	Positive: father and cousin with OMA	157 m	Ataxia	Learning difficulties ADHD	Speech therapy Psychology Occupational therapy
4	11 m	20 m	Negative	160 m	Ataxia	ADHD Behavioral difficulties	Psychology Occupational therapy Physical medicine and rehabilitation
5	5 m	7 m	Negative	21 m	OMA	Normal	-
7	4 m	5 m	Negative	18 m	OMA	Normal	Occupational therapy
9	12 m	20 m	Negative	168 m	Ataxia Dysarthria	Language delay Learning difficulties	Speech therapy Occupational therapy Physical medicine and rehabilitation
15	11 m	11 m	Positive: cousin with OMA	34 m	OMA	Language delay	Speech therapy Occupational therapy

Legends:*Findings in the follow-up; ADHD- attention deficit hyperactivity disorder; m- months; OMA – Oculomotor apraxia

Discussion

OMA is an uncommon disorder of ocular motility, often presenting as a manifestation of various underlying neurological, systemic, and genetic conditions [1-12]. Our study underscores the diverse etiological spectrum of OMA, ranging from neurologic disorders to metabolic diseases and chromosomal abnormalities [5-9]. The clinical evolution and the presence of associated neurological signs serve as crucial indicators for directing the etiological investigation, guiding clinicians towards a comprehensive diagnostic approach [1-2]. In the absence of identifiable causative factors, idiopathic OMA emerges as a diagnosis of exclusion [6]. Our findings align with existing literature [4], as the diagnosis of idiopathic OMA was predominantly established within the first year of life, with two cases of family history. Notably, familial cases of OMA were observed in around 10% of patients [4], highlighting the importance of genetic and familial history assessment in the diagnostic process. The most common neurological indicators at the time of referral were hypotonia and OMA, underscoring the significance of careful follow-up and the difficulties in detecting OMA. Etiological investigations yielded normal results, underscoring the complexity and multifactorial nature of idiopathic OMA [1-8]. Brain MRI may reveal subtle structural changes, as observed in one case, consistent with previous publish cases [2-3].

GDD emerged as a common finding among patients with OMA in our study, with language disorder and learning difficulties being predominant manifestations, followed by ADHD in two cases. While the frequency of GDD in OMA remains unknown [2-4], our study underscores the importance of early diagnosis and intervention, emphasizing the need for referral to specialized therapies and support services.

There are several limitations to our study. Primarily, the assessment of developmental delay was determined from a retrospective analysis of medical records, and some relevant information may be missing. School performance and cognitive scores could not be assessed in all preschool-aged patients during the last evaluation. Furthermore, considering the rarity of this condition, the study has a limited number of participants, which could affect the extrapolation of the findings to the rest of the population.

Conclusion

Idiopathic OMA poses a diagnostic challenge, requiring exclusion of other causes, with early identification facilitating management of developmental delay.

Research into genetic factors remains pivotal, as the familial association, the presence of subtle structural changes on brain MRI, and the occurrence of GDD collectively suggest underlying genetic changes yet to be elucidated, underscoring the ongoing need for further research into the genetic mechanisms underlying OMA.

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