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OCULOPALATAL TREMOR: A SISTEMATIZED REVIEW ON CLINICAL SPECTRUM, PATIENT GUIDANCE AND TREATMENT OUTCOME

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OCULOPALATAL TREMOR: A SISTEMATIZED REVIEW ON CLINICAL SPECTRUM, PATIENT GUIDANCE AND TREATMENT OUTCOME

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Abstract

Oculopalatal tremor (OPT) is a rare late complication following a disruptive lesion in the Guillain-Mollaret triangle (GMT). Literature on OPT diagnosis and treatment is scarce and heterogeneous, and lacks standardized assessment of visual function, oscillopsia, associated neurological involvement, diagnosis, patients' follow-up, and treatment outcome. In this work, we provide a state-of-the-art and systematized review based on the available literature and on our own experience, focusing on the mechanism, clinical spectrum and treatment outcome of OPT, seeking to identify main knowledge gaps and establish potential future research lines.

Methods: A Pubmed review on the english-based OPT literature was performed with no restrictions on time of publication. Additionally, data from OPT patients observed in our Neuro-Ophthalmology Clinic from 1 January 2015 to 31 December 2018 was provided in a separate series. Clinical and demographic variables including, age, gender, time to inaugural OPT symptom(s) and diagnosis, OPT etiology, nystagmus features and additional ocular motor signs, visual acuity (VA), presence of oscillopsia, palatal tremor, auditory click and fasciobrachial involvement, neuroimaging features, and treatment outcomes were collected. Descriptive statistics were performed using SPSS Statistics Software, (version 25.0; SPSS Inc., USA).

Results: A total of 140 patients were included (mean+/-SD age, 51,7+/-14,2 years; 92 males, 67,6%). Symptom(s) leading to OPT diagnosis included oscillopsia (33,3%), diplopia (28,5%), and imbalance (19,0%). Mean time from initial insult to symptom onset and from there to diagnosis was around 3 years (ie, 13,9+/-15,1 and 22,7+/-30,9 months, respectively). Main OPT causes included stroke (61%) [mainly hemorrhagic (74,6%)], arterio-venous malformation (12,2%), progressive ataxia and palatal tremor (7,3%), and post-surgery complication (4,9%). OPT nystagmus was predominantly pendular and oblique (57,5%), with a mean frequency of 2+/-0,51 Hz, frequently binocular (93,8%), asymmetric between eyes (62,7%), and associated with greater inferior olivary nucleus (ION)

hypertrophy on the side of the eye showing smaller amplitude nystagmus (64,2%). Associated ocular motor signs were frequently present (81,4%), VA was often reduced in one or the two eyes (77,7%), albeit only associated with oscillopsia in 44% of cases. Oscillopsia was almost universal (95,2%), PT was frequent (88,7%) albeit asymptomatic (91,7%), auditory click was infrequent (33,3%), and there was fasciobraquial involvement in 87,9% of cases. T2 weighted MRI of the ION showed either bilateral (40,6%) or unilateral (53,5%) ION hypertrophy, cerebellar atrophy (23,5%), and a GMT causative lesion that was predominantly located at the pontine level (60,9%) and absent (12,1%), mostly in neurodegenerative disorders. Reimaging still showed ION hypertrophy in the majority of cases (84,6%), and occasionally, new onset cerebellar atrophy (15,3%) in patients with focal GMT lesions. Non-placebo-controlled studies using gabapentin 300-1200mg/day (43%), memantine 20-40mg/day (30%), and clonazepam 0,125-1mg/day (33,3%) were associated with partial improvement in 54,5%, 66,7% and 50% of cases, respectively. Treatment outcomes chosen were heterogenous, including reduction of nystagmus or oscillopsia, improvement in visual acuity and nystagmus velocity, and subjective visual improvement. Mean re-evaluation time after treatment was 2,4+/-3,3 months.

Conclusion: The following are potential research venues in OPT: (1) Identification of factors playing a role in OPT diagnosis delay; (2) Mechanisms of hemorrhagic stroke in OPT; (3) Prevalence and progression of oscillopsia and reduced vision in OPT and their impact on quality of life; (4) The development of cerebellar atrophy following OPT due to a focal GMT lesion and (5) Placebo-controlled treatment trials with long-term follow-up in OPT.

Keywords

Oculopalatal Tremor; Guillain-Mollaret Triangle; Inferior Olivary Nucleus; Palatal Tremor; Nystagmus Treatment

Resumo

O Tremor Oculopalatino (TOP) é uma complicação rara e tardia de uma lesão estrutural a nível do Triângulo de Guillain-Mollaret (TGM). A literatura atual relativa ao diagnóstico de TOP é escassa e heterogénea, não existindo uma análise sistematizada da função visual, presença de oscilópsia, sinais neurológicos associados, diagnóstico, seguimento e opções terapêuticas. Com o presente trabalho pretende-se realizar uma revisão sistematizada baseada na literatura e também na nossa experiência clínica, focando-se no mecanismo, espectro clinico e resultado do tratamento do TOP, com o objetivo de identificar as lacunas existentes no conhecimento atual e determinar possíveis linhas de investigação futuras.

Métodos: Revisão da literatura de língua inglesa existente na base de dados *Pubmed,* sem restrição temporal relativamente à data de publicação dos estudos. Adicionalmente, foram revistos os processos clínicos dos doentes seguidos na clínica de Neuro-Oftalmologia do serviço de Neurologia do Centro Hospitalar e Universitário de Coimbra com o diagnóstico de TOP, observados entre 1 de Janeiro de 2015 e 31 de Dezembro de 2018. Foram recolhidos dados relativos às variáveis clínicas e demográficas, incluindo: idade, género, período de tempo até ao início dos sintomas de TOP e até ao diagnóstico, etiologia do TOP, caraterísticas do nistagmo, sinais oculares motores associados, acuidade visual, presença de oscilópsia, tremor do palato, *click* auditivo e envolvimento fascio-braquial, caraterísticas da neuro-imagem e resultados da terapêutica. A análise estatística foi realizada com recurso ao programa *SPSS Statistics Software*, (versão 25.0; SPSS Inc., USA).

Resultados: Foram incluídos 140 doentes (idade média+/-DP, 51,7+/-14,2 anos; 92 homens, 67,6%). Os sintomas iniciais de TOP incluíram oscilópsia (33,3%), diplopia (28,5%)

e desequilíbrio (19,0%). O tempo médio decorrido entre o insulto inicial e o início dos sintomas que levaram ao diagnóstico de TOP, e daí até ao diagnóstico deste foi cerca de 3 anos (13,9+/-15,1 e 22,7+/-30,9 meses, respetivamente). As causas principais de TOP foram o acidente vascular cerebral [maioritariamente hemorrágico (74,6%)], malformações arterio-venosas (12,2%), ataxia progressiva e tremor do palato (7,3%) e complicação pós-cirúrgica (4,9%). O nistagmo do TOP foi descrito como predominantemente pendular e oblíquo (57,5%), com uma frequência média de 2+/-0,51 Hz, geralmente binocular (93,8%), assimétrico (62,7%) e associado a maior grau de hipertrofia do núcleo olivar inferior (NOI) ipsilateral ao lado do olho com menor amplitude de nistagmo (64,2%). Foram identificados outros sinais oculares motores em 81,4% dos casos, e a acuidade visual encontrava-se diminuída mono ou binocularmente em 77,7% dos casos; contudo, esta apenas foi associada com a oscilópsia em 44%. A presença de oscilópsia foi quase universal (95,2%) e o tremor do palato estava presente em 88,7% dos doentes, embora descrito como assintomático em 91,7%. O *click* auditivo foi menos frequentemente relatado (33,3%), enquanto que o envolvimento de músculos faciais e braquiais foi reportado em 87,9% dos casos. A ressonância magnética em ponderação T2 dirigida ao NOI permitiu identificar hipertrofia uni (53,5%) ou bilateral (40,6%) do NOI, atrofia cerebelosa (23,5%), e presença de uma lesão causativa do TOP a nível do TGM, geralmente com localização pontina (60,9%), ou a sua ausência (12,1%), principalmente em casos de patologia neurodegenerativa. A repetição de ressonância permitiu demonstrar a manutenção da hipertrofia do NOI na maioria dos casos (84,6%) e ocasionalmente o aparecimento de atrofia cerebelosa de novo (15,3%) em doentes com lesões focais do TGM. Estudos não controlados por placebo com gabapentina 300-1200mg/dia (43%), memantina 20-40mg/dia (30%) e clonazepam 0,125mg-1mg/dia (33,3%) foram associados a uma melhoria parcial em 54,5%, 66,7% e 50% dos casos, respetivamente. Demonstrou-se uma marcada heterogeneidade dos *outcomes* clínicos, que incluíram redução da velocidade do nistagmo ou da oscilópsia, melhoria da acuidade visual e da velocidade do nistagmo, e melhoria visual subjetiva. O tempo médio de reavaliação após tratamento foi de 2,4+/-3,3 meses.

Conclusão: Constituem potenciais questões de investigação futura no TOP as seguintes: (1) Identificação dos factores envolvidos no atraso diagnóstico de TOP; (2) O mecanismo fisiopatológico do OPT na hemorragia do tronco encefálico; (3) A prevalência e progressão da oscilópsia e diminuição da acuidade visual no TOP, e o impacto destas na qualidade de vida; (4) O desenvolvimento de atrofia cerebelosa após TOP devido a lesão focal do TGM e (5) Ensaios clínicos farmacológicos controlados por placebo usando um longo período de seguimento.

Palavras- chave:

Tremor Oculopalatino; Triângulo de Guillain-Mollaret; Núcleo olivar inferior; Tremor do palato; Tratamento do nistagmo

Introduction

Oculopalatal tremor (OPT) is a rare delayed complication of a disruptive lesion in the Guillain and Mollaret's triangle (GMT) (1). It consists of an acquired involuntary eye oscillation (commonly called nystagmus) that may extend to the soft palate and other brachial arch muscles (eg, facial, buccal, neck, laryngeal and diaphragmatic muscles) (2,3).

Since its first description by Spencer in 1886, OPT's mechanism has been a matter of debate (4). GMT circuitry includes the cerebellar dentate nucleus (DN) and the contralateral inferior olivary nucleus (ION) and red nucleus (RN). Specifically, GABAergic inhibitory neurons originated in the DN travel through the superior cerebellar peduncle to reach the contralateral RN, where they join the central tegmental tract on its way to the ipsilateral ION. From ION, output is sent back to the DN via the inferior cerebellar peduncle (2). Any interruption occurring along the aforementioned circuit can theoretically leave the ION free to oscillate and to consequently enlarge, resulting in OPT. Indeed, ION hypertrophy seems to be present in the majority of OPT patients (5). Recent theories have challenged this view, focusing on the cerebellar role in the generation of OPT (6).

OPT manifests heterogeneously, and its causes are protean, including brainstem hemorrhage and infarction (7). Accordingly, ocular nystagmus in OPT can be vertical, horizontal, or oblique/ellipsoid, pendular or jerk, dissociated and/or disconjugated between eyes, demonstrating varying amplitude and/or velocity in each patient, oscillating between 2-3 HZ, and causing mild to severe and often distressful oscillopsia (ie, oscillation of the visual scene) (2,3). Indeed, anecdotal evidence has shown that visual dysfunction in OPT might have an high impact in patients' quality of life (8), when associated with a poor clinical outcome (6).

Currently, there is no strong evidence for an effective treatment in OPT, and treatment strategies anecdotally reported up to date, including the use of memantine and gabapentin, seem to fall short on clinical efficacy (6).

In this work, we provide a state-of-the-art and systematized review based on the available literature and on our own experience, focusing on the mechanism, clinical spectrum and treatment outcome of OPT, seeking to identify main knowledge gaps and to further establish the research lines deserving further investigation in the future.

Methods

Data Collection

An electronic search to review the OPT literature was performed in Pubmed with the keywords “oculopalatal tremor” OR “oculopalatal nystagmus” “oculopalatal myoclonus” OR “oculopalatal” OR “oculo-palatal”. No restrictions were made on time of publication. For the included articles, reference lists within the article and the “related articles” function on PubMed were also assessed for possible additional inclusions. Based on the articles included, a retrospective chart review of all patients was performed. English-based literature was collected. Reviews and articles with insufficient information were excluded. Additionally, data from all OPT patients referenced to our Neuro-Ophthalmology Clinic (Neurology Department, Coimbra University Hospital Center, Coimbra, Portugal) from 1 January 2015 to 31 December 2018, was provided in a separate series.

Study Variables

The following clinical and demographic data was collected: Age and gender; Symptom(s) leading to OPT diagnosis; Event to symptom interval (ie, lag time between the neurological event and probable symptom onset, in months); Symptom to diagnosis interval (ie, lag time between probable symptom onset and OPT diagnosis, in months); Event to diagnosis interval (ie, lag time between the neurological event and OPT diagnosis, in months); Etiology (ie, hemorrhagic stroke, ischemic stroke, arterio-venous malformation [AVM], progressive

ataxia and palatal tremor [PAPT], post-surgical complication, and other, including multiple sclerosis [MS], Alexander's disease, abscess, infectious, trauma, tumor, neurosarcoidosis, neuro-Behçet, vasospasm, vertebral artery dolichoectasia, and radiation).

The following nystagmus features were included: Direction (ie, horizontal, vertical, torsional, and mixed); Frequency (Hertz); Binocular vs. monocular; Amplitude symmetry and side predominance. Additional ocular motor signs were also searched, including gaze palsy, ocular motor palsy, saccadic intrusions [saccadic pulses, macrossacadic oscillations], gaze evoked nystagmus, hypermetric saccades, skew deviation, and one and a half syndrome. Visual acuity at the time of OPT diagnosis and presence of oscillopsia were also recorded.

The presence or absence of palatal tremor (PT) was further evaluated. If present, aspects including symmetry, synchrony with nystagmus and either if it was symptomatic or not, were additionally studied. The presence of facial, cervical, trunk and/or limb involvement, and perception of auditory click was also searched.

Neuroimaging variables included: T2-wheighted magnetic resonance imaging (MRI) results (ie, presence vs. absence of ION hypertrophy, symmetry vs. asymmetry of ION hypertrophy, presence vs. absence of cerebellar atrophy and most affected side, if asymmetric; presence vs. absence of a causative lesion in GMT, and specific location); Symptom to MRI (ie, lag time between probable symptom onset and MRI acquisition, in months); Event to MRI (ie, lag time between the neurological event and MRI acquisition, in months). If subsequent MRI was performed, data from the same variables was retrieved.

If treatment trial for OPT was initiated with one or more of the following interventions, ie, gabapentin, memantine, baclofen, clonazepam, botulinum toxin, surgery, immunosuppression, and/or deep brain stimulation (DBS), treatment outcome and post-treatment follow-up time were recorded, when available.

Statistical Methodology

Descriptive statistics were performed using SPSS Statistics Software, (version 25.0; SPSS Inc., USA). Quantitative variables were reported as mean, standard deviation, and range.

Results

Fifty-nine articles were included. Of those, 21 were excluded based on the above-mentioned criteria (ie, reviews [7], insufficient data [6], non-english language [8]), remaining 38 articles (see supplemental material). From these, a total of 140 patients were included. The mean age was 51,7 years (SD 14,2; range 12-86; n=124). There were 92 males (67,6%) and 44 females (32,4%) (n=136). Symptom(s) leading to OPT diagnosis (n=21) included related and non-related symptoms: oscillopsia (n=7; 33,3%), diplopia (n=6; 28,5%), imbalance (n=4; 19,0%), dysphagia (n=2; 0,9%), non-specific visual complaints (n=2; 0,9%), involuntary facial (n=1; 0,4%), limb (n=1; 0,4%) and eye (n=1; 0,4%) movements, and dysarthria (n=1; 0,4%). Event to symptom mean interval in these patients was 13,9 months (SD 15,1; range 0,5-48 months; n=21). Symptom to diagnosis mean interval was 22,7 months (SD 30,9; range 0-114 months; n=22). Event to diagnosis mean interval was 32,4 months (SD 36,9; range 0-192 months; n=42). The leading cause of OPT (n=123) was stroke (75; 61% - 56 hemorrhagic, 15 ischemic, and 4 unspecified), followed by AVMs (15; 12,2%), PAPT (9; 7,3%), and post-surgery complication (6; 4,9%). Other causes accounted for the remaining 18 (14.6%) cases (see table 1).

Nystagmus direction (n=108) showed a predominance of pure vertical (32; 29,6%), followed by pure torsional (8; 7,4%) and pure horizontal nystagmus (6; 5,6%). Mixed forms accounted for the majority of cases (62; 57,5%) cases. Nystagmus mean frequency (n=67) was 2 Hz (SD, 0,51 Hz; range, 0.7-8 Hz). In 75/80 (93,8%) patients, nystagmus was present in both eyes. Nystagmus amplitude was asymmetric between eyes in 47/75 (62,7%) patients.

Among these, the predominant side was the right side in 15 (20%), left side in 13 (17,3%), and not specified in the remaining cases. In asymmetric nystagmus cases (n=28), 18 (64,2%) patients had greater ION hypertrophy on the contralateral side, 2 (7,1%) on the ipsilateral side, 4 (14,2%) had symmetrical ION hypertrophy, and in 4 (14,2%), this was not specified. In symmetric nystagmus cases (n=28), 11 (39,2%) patients had symmetrical ION hypertrophy, 11 (39,2%) patients had asymmetrical or unilateral ION hypertrophy, and in 6 (21,4%), this was not specified.

Seventy nine out of 97 (81,4%) OPT patients had associated ocular motor signs, including one and a half syndrome, gaze palsy, impaired smooth pursuit and saccades, skew deviation, and gaze-evoked nystagmus (see table 2). Visual acuity at the time of OPT diagnosis was reduced in one or the two eyes of 14/18 patients (77,7%) studied. Only in 8/18 (44,0%), was visual impairment considered to be a consequence of OPT oscillopsia (see table 3). The latter symptom was present in the majority (60/63; 95,2%) of patients in whom it was actively searched.

Simultaneous PT was present in 94/106 (88,7%) patients. In 28/37 (75,7%), PT was further classified as symmetric. Twelve patients were inquired about the presence PT symptoms. Only 1 (8,3%) had symptomatic PT, describing it as a “throbbing sensation” in her throat. PT and nystagmus were synchronous in 39/47 (83%) patients studied. There was additional involvement of the limbs, face, chin or perioral muscles in 29/33 (87,9%) patients studied. Two out of 6 (33,3%) patients noticed an auditory click.

T2 weighted MRI of the ION (n=101) at the time of OPT diagnosis showed bilateral ION hypertrophy in 41 (40,6%), unilateral ION hypertrophy in 54 (53,5%) (right ION hypertrophy, 25; left INO hypertrophy, 29), and no ION hypertrophy in 5 (4,9%) patients. In 1 patient it was impossible to distinguish the ION due to superimposed hemorrhage. Cerebellar atrophy was actively confirmed or negated in 34/101 MRI cases. Eight out of 34 (23,5%) patients in whom cerebellar atrophy was actively confirmed or negated, showed additional signs of cerebellar atrophy. Symptom to MRI mean interval was 14,1 months (SD 23,0 months; range 12-84

months; n=14) and event to MRI mean interval was 20,8 months (SD 22,9 months; range 2-84 months; n=25).

In 115/140 (82,14%) patients, there was an initial lesion in OPT, which was located in the brainstem in the majority of cases (105/115; 91,3%), most commonly in pons (ie, Pons, 64; Pontomesencephalic junction, 3; Mesencephalon, 1; Not specified, 37). In 3 of these patients, the lesion extended to the cerebellum. Five/115 (4%) patients showed an isolated cerebellar lesion (the specific location was not specified). In other 5/115 (4%) patients, lesion location was not specified. In 17/140 (12,1%) patients, no particular focal lesion was found, for the majority in the context of probable degenerative disease (ie, PAPT ,9; Radiation, 2; Alexander's disease, 1; Multiple Sclerosis, 1; Encephalitis, 1; Viral encephalitis, 1; Behçet's disease, 1; Idiopathic, 1).

When imaging was repeated (n=13), 11/13 (84,6%) patients still evidenced ION hypertrophy, and 2/13 (15,3%) patients now had signs of cerebellar atrophy (there was no further mention on to whether asymmetric vs. generalized atrophy was present). One patient in particular, was reimaged twice, showing persistency of ION hypertrophy in the first reimaging 2 years after the insult, and ION atrophy in the second reimaging 4 years after the insult. In 2/13 (15,3%) patients, ION hypertrophy was absent, 7 and 2 years after the onset of symptoms. Of note, from the 10 patients showing cerebellar atrophy (2 only on reimaging), while 7 were associated with a neurodegenerative disorder, ie, PAPT, 3 had an isolated brainstem lesion in the GMT. Symptom to 2nd MRI mean interval was 36,6 months (SD 25 months; range 6-84 months; n=9) and event to 2nd MRI mean interval was 57,5 months (SD 54,4 months; range 19-96 months; n=2).

In 30 patients, OPT treatment was detailed, including gabapentin 300-1200mg/day (n=13; 43%), memantine 20-40mg/day (n=9; 30%), baclofen (dosage not specified) (5; 16,7%), clonazepam 0,125-1mg/day (n=10; 33,3%), rectus muscle and microvascular decompression of the vertebral artery surgery (n=5, n=1, respectively; 20%), botulinum toxin (n=5; 16,7%),

immunosuppression (3; 10%) and red nucleus DBS (1; 3,3%). In 12/30 (40%) patients, polytherapy was used, due to lack of efficiency with the first drug.

Treatment response was assessed in 21 patients (see table 4). Improvement was noted in 13 (61,9%) patients using one or more interventions, namely in 6/11 (54,5%), 4/6 (66,7%), 1/4 (25%), 3/6 (50%), and 2/3 (66,6%) patients under gabapentin, memantine, baclofen, clonazepam and immunosuppression, respectively, 3/4 (75%) patients undergoing surgery, and 3/4 (75%) undergoing botulinum toxin. DBS was tried in 1 case after multiple therapeutical trials and it failed. Treatment outcome was based on the reduction of nystagmus amplitude (n=2), subjective improvement in oscillopsia (n=2), visual acuity and nystagmus velocity (n=4), and subjective visual improvement (n=5). Mean re-evaluation time (n=14) was 2,4 months (SD 3,3 months, range 0,5-12 months).

We observed 7 additional OPT patients in our clinic, from 2015 to 2018 (see table 5). The mean age was 60,43 years (SD 9,3 years, range 59-83 years). There was 1 male (14,3%) and 6 females (85,7%). Event to symptom mean interval was 7,6 months (SD 6,3 months; range 1-16 months; n=5). Symptom to diagnosis mean interval was 30,17 months (SD 39,3 months; range 4-108 months; n=5). Event to diagnosis mean interval was 43,2 months (SD 42,0; range 7-120 months; n=5). The leading cause of OPT (n=7) was hemorrhagic stroke (6; 85,7%; in 4 of these patients there was an underlying cavernoma), followed by AVM (1; 14,3%). Nystagmus direction showed a predominance of pure vertical pendular nystagmus (4; 57,1%), Mixed forms accounted for the remaining 3 (42,9%) cases. Nystagmus mean frequency was 2,3 Hz (SD 0,67 Hz; range, 1,40–3,5 Hz), and it was present in both eyes in all patients, albeit with different amplitude between eyes in all. The predominant side was the right side in 4 (57,1%) patients. Five out of 7 (71,4%) OPT patients had associated ocular motor signs (see table). Best corrected visual acuity at the time of OPT diagnosis was reduced in one or the two eyes in all patients. Only in one (14,3%) patient, visual impairment was not considered to be a consequence of OPT oscillopsia. The latter symptom was present in the majority of patients (5/7; 71,4%). Simultaneous PT was present in all patients.

Only 1 patient (14,3%) had symptomatic PT. There was additional involvement of the limbs, face, chin or perioral muscles in 3/7 (42,9%) patients studied. One out of 7 (14,3%) patients noticed an auditory *click*. T2 weighted MRI of the ION (n=5) at the time of OPT diagnosis showed bilateral ION hypertrophy in 2 (40,0%) and unilateral ION hypertrophy in 3 (60,0%) patients (right ION hypertrophy, 2; left INO hypertrophy). One (20,0%) patient showed additional signs of cerebellar atrophy, predominant in the contralateral side of the GMT lesion. The initial lesion was located in the brainstem in 6 of the cases, most commonly in the pons (Pons, 5; Pontomesencephalic junction, 1). In 1 of these patients, the lesion extended to the cerebellum. One (14,3%) patient showed an isolated cerebellar lesion, located at the right cerebellar hemisphere, apparently involving the DN. In 4 patients, OPT treatment included gabapentin 300-900mg/day (n=2; 28,6%), baclofen 10mg/day (1; 14,3%), clonazepam 1-1,5mg/day (n=2; 28,6%). In their history, none of the interventions led to OPT's improvement, in terms of subjective visual improvement.

Tables and Figures

Table 1. OPT Etiology.

Etiology	Patients (n=123)	Relative percentage %
Hemorragic stroke	56	45,5
Ischemic stroke	15	12,2
Arteriovenous malformation	15	12,2
PAPT	9	7,3
Post-surgery complication	6	4,9
Tumour	5	4,1
Stroke*	4	3,3
Post-radiation complication	2	1,6
Abscess	1	0,8
Alexander's disease	1	0,8
Encephalitis	1	0,8
Idiopathic	1	0,8
Multiple sclerosis	1	0,8
Neuro- Behçet	1	0,8
Neurosarcoidosis	1	0,8
Trauma	1	0,8
Vasospasm	1	0,8
Vertebral artery dolichoectasia	1	0,8
Viral encephalitis	1	0,8

*Stroke type not detailed; PATP, Progressive Ataxia and Palatal Tremor; OPT, Oculopalatal Tremor

Table 2. Associated ocular motor signs in OPT.

Ocular motor signs in OPT	Frequency	Percentage % (n=79)
One and a half syndrome	26	32,91
Gaze palsy	25	31,64
Impaired smooth pursuit	13	16,46
Hypermetric saccades	11	13,92
Skew deviation	10	12,66
Gaze evoked nystagmus	9	11,39
Exotropia	6	7,59
Ocular Bobbing	6	7,59
6th nerve palsy	6	7,59
Decreased VOR gain	6	7,59
Impaired VOR suppression	5	6,33
Internuclear ophthalmoplegia	5	6,33
Esotropia	4	5,06
Macrossaccadic oscillations	2	2,53
Dysmetric saccades	2	2,53
Ptosis	2	2,53
3rd nerve palsy	2	2,53
Square wave jerks	2	2,53
Increased VOR gain	2	2,54
Double saccadic pulses	1	1,27
7th nerve palsy	1	1,27
4th nerve palsy	1	1,27
Afferent pupillary defect	1	1,27
Horner's syndrome	1	1,27
Blepharospasm	1	1,27
Vertical strabismus	1	1,27

VOR, Vestibulo-ocular reflex; OPT, Oculopalatal tremor

Table 3. Visual acuity in OPT.

Patient	OD	OS	Related cause
1 Talks and Elston. 1997	-	6/36	Oscillopsia
2 Talks and Elston. 1997	6/36	6/36	Oscillopsia
3 Danesh-Meyer. 2002	20/60	20/25	-
4 Sudhakar et al. 2012	20/25	CF	-
5 Graber et al. 2016	20/100	20/100	Oscillopsia
6 Graber et al.2016	60/100	60/100	Oscillopsia
7 Graber et al. 2016	50/100	50/100	Oscillopsia
8 Graber et al. 2016	100/100	100/100	-
9 Graber et al. 2016	20/100	20/100	Oscillopsia
10 Repka et al. 1994	20/80	-	Oscillopsia
11 Repka et al. 1994	20/200	20/200	Oscillopsia
12 Papachatzaki et al. 2013	20/60	20/80	-
13 Vanikieti et al. 2016	20/20	20/20	-
14 Cackett et al. 2002	6/18	6/6	AACG OD
15 Massry and Chung. 1994	20/30	20/30	-
16 Samuel et al. 2004	20/20	20/20	-
17 Samuel et al. 2004	100/100	100/100	-
18 Samuel et al. 2004	100/100	100/100	-

(-), Not provided; CF, Counting fingers; AACG, Acute angle closure glaucoma; OPT, Oculopalatal Tremor

Table 4. Treatment Outcomes in OPT.

Treatment	Patients (n=21)			Total
	Partial improvement	Full improvement	No improvement	
Gabapentin Jang and Borruat 2014; Murdoch et al. 2016; Wang et al. 2009; Aladdin et al. 2008; Sato et al. 2018; Eggenberger et al. 2001; Morgan et al. 2015; Thurtell et al. 2010	6	0	5	11
Memantine Jang and Borruat. 2014; Murdoch et al. 2016; Thurtell et al. 2010	4	0	2	6
Baclofen Shaikh et al. 2010; Murdoch et al. 2016; Thurtell et al. 2010	1	0	3	4
Clonazepam Murdoch et al. 2016; Wang et al. 2009; Aladdin et al. 2008; Sato et al. 2018; Eggenberger et al. 2001	3	0	3	6
Rectus muscle surgery Sidiropoulos et al. 2014; Talks and Elston. 1997; Danesh-Meyer. 2002	3	0	0	3
Microvascular decompression Vanikieti et al. 2016	0	0	1	1
Botulinum toxin Talks and Elston. 1997; Wang et al. 2009; Repka et al. 1994	3	0	1	4
Immunosuppression Sidiropoulos et al. 2014; Sudhakar et al. 2012; Pfeffer et al. 2011	1	1	1	3
DBS Wang et al. 2009	0	0	1	1

DBS, Deep brain stimulation; OPT, Oculopalatal tremor

Table 5. OPT Series.

Pt. age/ sex	Etiology and location	Event to symptom (months)	Symptom to diagnosis (months)	Event to diagnosis (months)	Nystagmus direction	Nystagmus frequency (Hz)	Nystagmus amplitude	Additional oculomotor findings	Oscillopsia	Palatal tremor	Auditory click	Face, cervical and limb muscles involvement	MRI findings (ION hypertrophy, cerebellar atrophy)	OPT Treatment
59, F	Hemorragic stroke (ponto-mesencephalic cavernoma)	6	14	20	Horizontal OD Vertical OS	1,9	OD>OS	None	Yes	Yes	No	No	-	Gabapentin 300mg tid
83, F	Right cerebellar hemisphere AVM	-	-	12	Pure vertical OU	2,4	OD>OS	Gaze-evoked nystagmus, hypermetric saccades	Yes	Yes	No	Yes	Bilateral ION hypertrophy	None
67, F	Hypertensive hemorragic stroke (pons)	12	108	120	Pure vertical OU	3,5	OD<OS	One and a half syndrome	Yes	Yes	Yes	No	Right ION hypertrophy and left cerebellar atrophy	Clonazepam 0,5mg bid Baclofen 10mg id
66, F	Hemorragic stroke (pontine cavernoma)	16	32	48	Pure vertical OU	2,4	OD>OS	Bilateral internuclear ophthalmoplegia	No	Yes	No	Yes	Right ION hypertrophy	Clonazepam 0,5mg tid
59, F	Hemorragic stroke (pontine cavernoma)	3	4	7	Pure vertical OU	1,4	OD>OS	Gaze palsy, gaze-evoked nystagmus, Internuclear Ophthalmoplegia	Yes	Yes	No	No	Left ION hypertrophy	Gabapentine 100mg tid
61, F	Hypertensive hemorragic stroke (pontine and cerebellar involvement)	-	-	52	Horizontal OU Vertical OS	2,4	OD<OS	Gaze-evoked nystagmus	No	Yes	No	Yes	-	None
77, M	Hemorragic stroke (pontine cavernoma)	1	11	12	Torsional and Vertical OU	1,8	OD>OS	None	Yes	Yes	No	No	Bilateral ION hypertrophy	None

(-) Not available; AVM, Arterio-venous malformation; OD, Right eye; OS, Left eye; OU, Both eyes; ION, Inferior olivary nucleus; OPT, Oculopalatal tremor

Discussion

OPT is the ultimate manifestation of an unfolding of events that begin with a disruptive lesion in the GMT, most commonly located in the brainstem. In this systematized review, OPT was more prevalent in men, with a mean age of 50 years old. This finding was rather expected, since stroke, particularly hemorrhagic stroke in the context of small vessel disease, which is more prevalent in middle age men, accounted for the majority of OPT cases (9). Importantly, this finding supports and replicates at a larger scale what others have found in small series (10). Nonetheless, it is intriguing to verify that hemorrhagic stroke, which in some series is associated with better functional recovery when compared with ischemic stroke, is actually more often associated with a longstanding ocular motor abnormality, ie, OPT. A better neurological recovery in hemorrhagic stroke has been ascribed to the mechanisms for neurological deficit from hemorrhagic stroke (ie, brain compression). As the hematoma resolves, neurological functions recover and functional status improves (11). Therefore, OPT's mechanism after hemorrhagic stroke does not seem to be exclusively related to the presence of edema/compression of GTM structures and other factors must play a role in its generation.

There was a 2-year mean interval between the initial OPT symptom(s) (eg, oscillopsia) and OPT diagnosis in the current series. This delay might reflect one of the several non-mutually exclusive factors: (1) presence of non-distressful/mild oscillopsia or no symptom at all, therefore not requiring medical attention; (2) diagnostic confusion between a new brainstem acute event versus the appearance of a late manifestation (ie, OPT) in the context of a previous brainstem insult; (3) OPT signs/symptoms overshadowed by other lesion-related symptoms (eg, marked ataxia, internuclear ophthalmoplegia, dysarthria, weakness, etc). Indeed, only a small number of studies reported the existence of an initial OPT-related or non-related symptom leading to the diagnosis, which suggests that OPT can be mild and/or asymptomatic in a substantial number of cases at least at an initial phase, and its detection may rather occur during follow-up examination of an acute brainstem event. Importantly, the

absence of OPT-related symptoms, ie, oscillopsia, vision loss, involuntary face, cervical and/or limb movements, should not preclude the active search of OPT by the clinician in these cases, since in the current series, the symptoms leading to OPT diagnosis were often non-related (eg, diplopia, imbalance). Still, particularly for clinicians, the data provided here stresses the importance of having a high degree of clinical suspicion for OPT, particularly in patients within 1 year after an initial brainstem insult, especially when a hemorrhage was the culprit.

Apart from vascular and other strategic focal brainstem lesions, PAPT was also a major cause of OPT in this series. In PAPT, OPT is associated with ataxia that gradually worsens. Degenerative brainstem or cerebellar disorders, including Alexander's disease and mitochondrial disorders are occasionally found as the underlying pathology (12). Contrary to most cases of OPT, in which the causative lesion is often located in the brainstem (see below), in sporadic PAPT, the exact location of the lesion in uncertain. Strikingly however, acquired focal brainstem lesions can also give rise to a PAPT phenotype, manifesting with progressive cerebellar atrophy after the initial insult, as seen in 3 cases in the current series. Therefore, not only is OPT already a late manifestation of a brainstem or cerebellar insult, but apparently it can also precipitate cerebellar atrophy and progressive ataxia. This is in line with recent theories stressing the putative role of the cerebellar maladaptive plastic process taking place in OPT when in presence of an abnormally high ION input to the contralateral DN (13) (see below). Why progressive ataxia only occurs in selected acquired OPT cases is not known (14). Importantly, while PAPT's cause remains undetermined in most patients, several genetic disorders are being increasingly linked to this phenotype, stressing the role of an extended investigation in OPT patients lacking a GTM acquired lesion, apart from ION hypertrophy (12).

The current series confirms the exclusive involvement of the brainstem in the large majority of OPT cases, specifically the pontine region involving the central tegmental tract (4). The mechanism underlying OPT is still largely unknown, thought. The only certainty is the

existence of a disruptive lesion in the GMT as a mandatory condition to precipitate OPT's appearance (1). One additional requirement for its generation is the need for an "oscillator", if one takes into account its characteristic pendular waveform, best seen in eye movement recordings (15). And according to the data provided here, a third requirement is based on the fact that DN, ION and their output fibers seem to be relatively spared by the initial/causative lesion in OPT cases, leaving the central tegmental tract (ie, comprised by the output fibers reaching the INO) as the critical target for generating OPT. Some unique features of the ION neurons make them the perfect candidate for harboring pathological oscillations. Indeed, ION neurons have a spontaneous tendency to oscillate (16). Additionally, they have dendro-dendritic gap junctions, which potentiates electrotonic coupling and allows them to share the same subthreshold membrane oscillations, ultimately promoting synchronicity of oscillations (17–20). Under normal circumstances, the DN and its output fibers are able to inhibit ION neurons' natural tendency to oscillate. If this inhibitory pathway becomes dysfunctional, not only the ION neurons will be free to oscillate, but they will also develop abnormal somato-somatic gap junctions that increase the electrotonic coupling strength (16). Abnormal ION neurons oscillatory activity is believed to cause INO hypertrophy, which was indeed found in large majority of the current series. ION T2 signal seems to change within a month after the initial GMT lesion, progressing to ION hypertrophy, the latter due to transsynaptic degeneration, resulting in acetylcholinesterase reaction products accumulation (5). ION hypertrophy may remain unchanged for years, as seen in our subgroup of reimaged patients (21). One additional mechanism for explaining the final appearance of OPT nystagmus waveform possibly relates to a maladaptive cerebellar response to the ION oscillatory input to the DN. Specifically, cerebellar Purkinje cells and interneurons pairs undergo a conditioning learning process during which they start to pause in between ION pulses. This putatively causes the large amplitude and smooth nystagmus waveform characteristically seen in OPT (ie, "cerebellar smoothing"), and may theoretically lead to progressive cerebellar atrophy and limb ataxia, particularly in the contralateral side of ION hypertrophy, according to a recent hypothesis (13). However, we were not able to find in the current literature series,

an OPT case associated with progressive ataxia in which cerebellar atrophy was documented as asymmetric and contralateral to ION hypertrophy. In our own small series however, we described one case supporting the aforementioned theory. Future volumetric studies need to address this question prospectively, in order to answer this question.

OPT presents as a mainly mixed pendular nystagmus, with the vertical axis more often involved, often being asymmetric between eyes. This large series helps supporting the view that asymmetric nystagmus forms in OPT are frequently associated with asymmetric or strictly unilateral ION hypertrophy, while symmetric forms may be associated with either asymmetric or symmetric ION hypertrophy. Asymmetric involvement of the feedback control of the eye velocity-to-position integrator, close to the ION, has been theoretically invoked as a mechanism for such finding (7).

The greater prevalence of horizontal supra and internuclear gaze palsies, skew deviation, and gaze evoked nystagmus in OPT in this series was rather expected, taking into account the close proximity between the central tegmental tract and the medial longitudinal fasciculus, paramedian pontine reticular formation, and the medial vestibular nucleus (22). The high prevalence of hypermetric saccades on the other hand probably reflects the OPT cases with initial or late cerebellar involvement (22).

A rather counter-intuitive finding in the current work, was the fact that while only in about one tenth of the patients were initial OPT-related or non-related symptoms leading to OPT diagnosis reported, the majority of patients in whom an OPT-related symptom (ie, oscillopsia) was actively searched, answered positively. While bias related to the retrospective nature of this work might be playing a role, oscillopsia might actually not constitute a presenting symptom in some OPT patients, and rather be highly prevalent late in the process, when nystagmus increasing amplitude supersedes the mechanisms responsible with keeping a stable visual perception (23). Patients with minimal oscillopsia probably remain asymptomatic and OPT diagnosis is based on the detection of asymmetric vertical pendular nystagmus during a routine or brainstem event follow-up examination.

Importantly, the current data shows that visual acuity seems to be reduced in OPT patients, albeit this finding has been anecdotally reported. From studies in other forms of nystagmus, we know that several visual functions are indeed impaired once retinal image motion exceeds 2 to 3°/second (eg, as in nystagmus from OPT patients), and poor visual function is associated with poor social function, ultimately affecting quality of life in various domains (24–26). Detailed visual function assessment and vision-related quality of life have in OPT are needed.

OPT treatment's results have been largely unsatisfactory, and their evidence for improvement is weak, as demonstrated in the current work. Patients often show only modest or no improvement under one or several drugs, the outcomes used are heterogenous and do not always correlate between each other (ie, documenting a post-treatment reduction in nystagmus waveform amplitude does not necessarily correlates with an improvement in visual acuity and/or quality of life), the re-evaluation times used (eg, 2 weeks) are very useful as a proof of concept but hardly reflect a real-life situation (ie, the drugs used so far lack long term follow-up), and finally, there are no placebo-control trials on OPT (27). One classic treatment option in OPT has been the use N-methyl-D-aspartate (NMDA) receptor antagonists such as gabapentin and memantine, to block ION and DN output. This has been associated with modest improvement in nystagmus speed and visual acuity. Unfortunately, both drugs can produce imbalance and lethargy, a fact that has to be taken into account in OPT patients, since they often show co-existent ataxia (27). Botulinum toxin and strabismus surgery, while effective in anecdotal series, are invasive, associated with important side effects, and lack long term follow-up (28). Importantly, future drugs for OPT should additionally target ION electronic coupling and block the somato-somatic gap juntions (eg. mefloquine), according to a recent theoretical model (13,29).

Our work has limitations. This was a retrospective analysis and therefore all variables had missing data. The key word's search used in the current series was mostly focused on searching for OPT cases in which nystagmus was a predominant feature, in order to better

characterize this population. This option might have missed the body of work focusing on cases with predominant palatal tremor in which eye movement component is nevertheless usually poorly or scarcely described.

The current work tried to identify knowledge gaps on OPT literature, ultimately aiming to steam new lines of research in OPT, including: (1) The high prevalence of hemorrhagic stroke in OPT needs further clarification; (2) Factors playing a role in the delay of OPT diagnosis need to be clearly identified; (3) The exact prevalence of oscillopsia and reduced vision in OPT, their progression over time, and their impact in the quality of life should be prospectively addressed; (4) Tardive ataxia following OPT due to a focal GMT lesion and the putative cerebellar asymmetric atrophy accompanying it, lack a plausible explanation, need stronger clinical evidence for supporting its occurrence, and this selected group of patients needs serial volumetric and metabolic imaging assessments; (5) Placebo-controlled treatment trials with long term follow-up are needed in OPT; (6) OPT mechanism, including ION electronic coupling and the investigation of potential OPT drugs that target electronic coupling, need further research. Importantly, data from our own small series mirrored almost every clinical and demographic aspect detailed in the systematized review.

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Supplemental material

Articles included in the review analysis

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