

Oculogyric crises: etiology, pathophysiology and therapeutic approaches

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Abstract

Oculogyric crisis (OGC) describes the clinical phenomenon of sustained dystonic, conjugate and typically upward deviation of the eyes lasting from seconds to hours. It was initially observed in patients with postencephalitic parkinsonism, but since then a number of conditions have been associated with OGC. These include drug-induced reactions, hereditary and sporadic movement disorders, and focal brain lesions. Here, we systematically review the literature and discuss the spectrum of disorders associated with OGC in order to aid clinicians place this rare but distinctive clinical sign into the appropriate diagnostic context. We also provide a brief synthesis of putative pathophysiological mechanisms, as well as therapeutic recommendations based on the literature and our own experience.

Introduction

Oculogyric crisis (OGC) is a rare neurologic manifestation characterized by sustained dystonic, conjugate and typically upward deviation of the eyes lasting from seconds to hours [1]. Oculogyric crises were first described in patients with parkinsonism following the epidemic of encephalitis lethargica (Economo's disease) during the 1910-1930s [2]. Since then, OGCs have been reported in association with numerous conditions, as for example drug-induced, but also neurometabolic and neurodegenerative movement disorders, or as a consequence of focal brain lesions [3-7].

Although commonly reported as acute disorder, OGC may also occur within weeks or even months after an inciting event [1, 8-10]. Clinical presentation may vary from very brief and subtle eye deviation as an isolated symptom to more severe and even painful forms accompanied by neck flexion, jaw opening, blepharospasm, tongue protrusion and autonomic signs, such as perspiration, pupillary dilation, increases in blood pressure and heart rate. Episodes generally last minutes, but may range from seconds to hours. In addition, psychiatric symptoms such as agitation and anxiety, but also psychotic symptoms including visual, tactile and auditory hallucinations, distortions of body schema, catatonic symptoms, mood disorders such as depression or mania and obsessive-compulsive behaviors may occur [3, 8, 11-14].

Oculogyric crises are not life threatening. However, they often present a source of distress for patients and their environment. Due to their rarity and variable clinical severity OGCs may be easily overseen or misinterpreted as functional or as exacerbation of psychotic illness [11, 13]. Oculogyric crises are non epileptic eye movements and should, therefore, be distinguished from more commonly occurring tonic eye deviations within the context of epileptic seizures (i.e. thorough history and clinical observation for features suggestive of an epileptic event and EEG), but also

from oculogyric tics, as part of tics disorders [15, 16]. Oculogyric crises should also be separated from the paroxysmal tonic upgaze syndrome characterized by infantile-/early childhood-onset and episodic tonic upward deviation of the eyes, neck flexion downbeating saccades in attempted downgaze and normal horizontal eye movements [17]. Indeed, the recognition of OGCs is a useful clinical sign to guide the diagnostic procedure, leading in turn to appropriate counseling and treatment. To date, there has been no systematic study to assess the spectrum of conditions reported to occur with OGCs and to provide a list of relevant diagnoses in such cases.

Methods

This review is based on a systematic search of the literature in PubMed (a service of the National Library of Medicine's National Center for Biotechnology Information; <http://www.ncbi.nlm.nih.gov>) for all publications up to March 2016 using the key words oculogyric eye movements, oculogyric crisis/crises, tonic eye deviation, tonic gaze deviation and all combinations of these. Only articles with publication of original clinical information and published in English were considered. Pertinent references cited in relevant articles and their bibliographies were also checked and considered if fulfilling the criteria for this review. After removal of articles without abstract, duplicates and opinions/comments about articles, all abstracts and full texts if available were reviewed. Articles without original, insufficient or inconsistent clinical information were excluded. All identified articles are referenced in supplement 1.

Results

According to our inclusion and exclusion criteria 147 publications reporting the clinical characteristics of 394 patients with OGCs were identified. Based on our results, three main aetiological categories were discerned: 1. Drug-induced OGCs; 2. Oculogyric

crises associated with hereditary and sporadic movement disorders; 3. Oculogyric crises as a result of focal brain lesions. Following, we present the clinical characteristics of patients of these three categories according to their reported frequency. Based on these data we also provide a synthesis of putative pathophysiological mechanisms and present recommended treatment strategies.

1. Drug-induced OGC

The majority of the reported OGC cases were drug-induced, most commonly as adverse effects of neuroleptics, antiemetics or other dopamine antagonists (complete list of drugs inducing OGCs is provided in table 1). Among the 175 reported patients the median age was 22 years (range: seven months to 54 years), with a 1:1 male/female ratio. Oculogyric crises usually disappeared within 24 to 48 h upon withdrawal or reduction of the antidopaminergic/neuroleptic medication.

Neuroleptics

Sixtyeight percent of all reported patients (median age: 24 years; range: five to 47 years) with drug-induced OGCs we could identify were due to neuroleptics. In this context OGCs were commonly described as an acute dystonic reaction usually occurring promptly after the administration, or less often, following long-term exposure to neuroleptics (i.e. OGC as a tardive dystonic reaction) [8, 18]. Both typical and atypical neuroleptics induced OGCs, however the use of typical neuroleptics and OGCs was more commonly reported (63 patients in 15 articles for typicals versus 32 patients in 21 articles for atypicals; the exact neuroleptic agent was not reported for 24 remaining cases). Younger age, male sex, dose increase of an existing pharmacological agent or the introduction of a new agent were reported as associated risk factors [19-22].

Antiemetics

We found nine articles reporting OGCs in ten female patients and one male patient (median age: 21 years; range: 13 to 55 years) receiving antiemetics. Oculogyric crises were reported in five patients following intake of metoclopramide [23-27], in three patients upon administration of phenothiazines [28] used as antiemetics, and also in single cases associated with intake of clebopride, ondansetron and droperidol [29-31].

Anticonvulsants

Thirteen patients in seven different articles were identified reporting OGCs as a result of treatment with anticonvulsants. The five male and five female patients (the gender of the remaining three patients was not reported) had a median age of 26 years (range: three to 33 years). Carbamazepine (six patients) [32-35], lamotrigine (four patients) [36], gabapentin (two patients) [37], and oxcarbazepine (one patient) [38] are described. All patients were treated for epilepsy with or without mental retardation. In most patients OGCs were terminated by dose reduction suggesting a dose-depending effect [33, 34, 36].

Antidepressants

Oculogyric crises were also reported in association with antidepressants (four articles, three female and one male patients; median age: 28 years; range: ten to 44 years). Three articles reported OGCs following intake of selective serotonin reuptake inhibitors (SSRIs; fluoxetine and citalopram, fluvoxamine, escitalopram) [39-41]. One article reported the induction of OGCs by imipramine, one of the first tricyclic antidepressants acting by inhibiting serotonin and noradrenaline reuptake [42].

Others

Further case reports and case series (13 articles, 24 patients; median age: 15 years; range: seven months to 54 years) described OGCs after intake of cetirizine (number of patients; n=9) [43], organophosphate poisoning (n=3) [44], tetrabenazine (n=2) [45, 46], L-dopa (n=2) [47], lithium (n=1) [48], tensilon (n=1) [49], cefexime (n=1) [50], pentazocine (n=1) [51], nifedipine (n=1) [52], isotretinoin (n=1) [53], phencyclidine (n=1) [54] and salicylate intoxication (n=1) [55].

OGC despite withdrawal or following discontinuation of medication

Oculogyric crises usually disappear within 24 to 48 h upon withdrawal or reduction of the triggering agent; and continuation of OGCs without further exposure is generally not seen.

Schneider and colleagues, however, observed OGCs in three patients in whom episodes of OGCs, initially triggered by a single dose of haloperidol (in two cases) or a single dose of metoclopramide (in one case), continued spontaneously despite withdrawal [9]. Oculogyric crises in these cases were successfully treated with anticholinergics.

On the other hand, Mendhekar and Duggal described a female patient with mental retardation and aggressive behavior who developed OGCs only after abrupt discontinuation of clozapine. This resolved upon recommencing the medication [56]. Oculogyric crises have also been described during off-periods of L-dopa treatment in two parkinsonian patients, which improved with increasing the dopaminergic medication [57, 58].

2. Hereditary and sporadic movement disorders

The second most common association of OGCs was with hereditary and sporadic movement disorders (complete list of all disorders is provided in table 2). In total 57

articles with 207 patients were identified with a median age of 23 years (two months to 92 years) and 1:1.3 male/female ratio (64 males, 83 females; 60 patients no gender reported).

Disorders of dopamine metabolism

Disorders of dopamine metabolism are the most common metabolic cause of OGCs, which may be a clue towards the pathophysiology (see below). The literature review revealed 103 cases (in 28 reports). This included deficiency of aromatic L-amino acid decarboxylase (AADC) (n=75 in 17 articles)[59-61], sepiapterin reductase (SR) [62-65] (n=19; median age: 10 years; range: three to 23 years), tyrosine hydroxylase (TH) [66-70] (n=7) and guanosine-triphosphate cyclohydrolase type I (GTPCH) [71] (n=1) or molecularly-undefined dopa-responsive dystonia (n=1) [72], all autosomal-recessive disorders with similar phenotypic features [4]. In more detail, for AADC, reported patients were mostly infants and children (median age: five years; range: two months to 33 years) and presented with early (neonatal) hypotonia, developmental delay, autonomic abnormalities, such as excessive sweating or temperature instability and OGCs. Associated movement disorders included parkinsonism, dystonia and/or chorea.

Other hereditary movement disorders

Oculogyric crises were reported in 22 female patients with Rett syndrome [73], six patients (median: nine years; range: three to 16 years) with mutations at the *SLC18A2* gene encoding the vesicular monoamine transporter 2 (VMAT2) in the presynaptic neurons [74, 75] and three cases of Kufor Rakeb disease due to mutations in *ATP13A2* [76, 77]. Further, OGCs were described in two cases with neuronal intranuclear inclusion disease (NIID) [78, 79]. Oculogyric crises have also been associated with neurodegeneration with brain iron accumulation due to mutations in *PLA2G6* [80] and

pantothenate kinase-associated neurodegeneration (PKAN) [81]. Interestingly, in the two cases of PLA2G6 neurodegeneration with brain iron accumulation, OGCs occurred in the dopaminergic ON state, and this has been suggested as a helpful clinical hint to differentiate this type of disorder from other brain iron accumulation syndromes [80].

Pathogenic mutations in *GRIN1* gene, encoding for the GluN1 subunit of the ionotropic glutamate N-methyl-D-aspartate (NMDA) are associated with an early onset dysmorphic syndrome, oculomotor abnormalities, epilepsy, spasticity and hyperkinetic movement disorders, to include chorea and myoclonus [82]. MRI images show structural abnormalities such as ventriculomegaly, thin corpus callosum and cerebral atrophy. Oculogyric crises have been described in two such cases [82].

Furthermore, single cases of OGCs were described in hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC) syndrome [83], rapid-onset dystonia parkinsonism due to mutations in the *ATP1A3* gene [84], Perry syndrome [85], Wilson's disease [5], Chédiak-Higashi syndrome [86] and ataxia-telangiectasia [87]. Also, OGCs were described in a patient with molecularly unclassified juvenile parkinsonism [88].

Sporadic movement disorders

Oculogyric crises in sporadic movement disorders were identified in 15 articles describing 59 patients. The majority of the identified articles reported OGCs in parkinsonian patients (number of patients: n=54; median age: 35 years; range: eight to 92 years), as a result of encephalitis lethargica (EL) (n=48) [14, 89-94], EL-like illness (n=1) [95] or Japanese Encephalitis (n=1) [96]. Oculogyric crises were further reported in patients with young-onset (n=1) [97] and juvenile onset parkinsonism (n=2) [88, 98], and due to subcortical arteriosclerotic encephalopathy (n=1) [99]. Blepharospasm (n=4)

[100] and non-wilsonian hepato-cerebral degeneration (n=1) [101] were also associated with OGCs. Movements described as OGCs have also been more recently described in patients with functional movement disorders [102].

3. Focal brain lesions:

Twelve single case reports of OGCs occurring as a result of focal brain lesions were also identified. They included lesions of the brainstem caused by herpetic encephalitis [7], the dorsal midbrain area (mesencephalic locomotor region) [103], the substantia nigra [6], the posterior third ventricle affected by a cystic glioma [104] and the basal ganglia [105, 106] [107]. Also two patients with either multifocal drug-induced encephalopathy or posterior leukencephalopathy syndrome were reported to develop OGCs [108, 109]. However, in both of these cases additional factors may have contributed to the development of OGCs. Finally, OGCs have also been reported most likely in association with focal lesions caused by neurosyphilis and multiple sclerosis [110].

Pathophysiology

The pathophysiology of OGCs remains elusive. However, despite the numerous conditions associated with OGCs and the diversity of clinical presentations, there appear to be common pathophysiological changes associated with the manifestation of OGCs. First, in all reviewed cases where OGCs were clearly a result of focal brain lesions, damage was reported either to the basal ganglia or the midbrain, and thereby related to possible anatomical disruption of the nigrostriatal pathway. Second, most agents related to drug-induced OGCs (e.g. neuroleptics or antiemetics) characteristically lead to a functional disruption of dopaminergic neurotransmission.

Third, most of the hereditary and sporadic movement disorders associated with OGCs are also directly related to either neurochemical (e.g. AADC and others [4]) or anatomical disruption of dopamine synthesis (e.g. through lesions or gliosis as for example in postencephalitic parkinsonism [111], Wilson's disease [5] or Perry syndrome [85]) and typically manifest with parkinsonian and/or dystonic symptoms. It, thus, appears that dopaminergic neurotransmission is at the pathophysiological epicentre of OGCs.

Considered within the frame of dystonic reactions (also referred to as “extraocular muscle dystonia” [100]), it has been often proposed that OGCs, as other acute drug-induced dystonias, could be the result of an imbalance between dopaminergic and cholinergic inputs within the striatum. Indeed, striatal dopaminergic input is known to suppress cholinergic tone [112, 113]. Dopaminergic hypofunction, particularly related to striatal dopamine D2 receptors of cholinergic interneurons, could lead to a relative increase of cholinergic neurotransmission within the striatum and alterations in excitation properties of medium spiny neurons leading to dystonic symptoms, including OGCs [114]. Clinical knowledge also lends support to this hypothesis, as anticholinergic drugs often lead to an amelioration of OGCs.

However, an imbalance between dopaminergic and cholinergic neurotransmission may not be the sole pathophysiological explanation for all OGC cases. For example, the pathophysiology of tardive OGCs, as of other tardive dystonic syndromes, might be different and more complex. Hypersensitivity of striatal dopamine receptors due to chronic dopamine receptor blockage, neurodegeneration of striatal interneurons, as well as dysfunction of striatal gamma-Aminobutyric acid (GABA)-ergic interneurons and more recently the hypothesis of maladaptive synaptic plasticity have been proposed to

explain the presence of tardive involuntary movements [115]. However, robust experimental data, including animal models of OGCs, to support either hypothesis in humans are lacking. Moreover, it is unclear, whether tardive OGCs share similar pathophysiological properties with other tardive syndromes, such as tardive dystonia.

Similarly, the pathophysiology of OGCs related to drugs, not directly associated with dopaminergic function, as for example SSRIs also remains unclear. Several hypotheses have been put forward, including hyperstimulation of 5-HT₂ receptors, inhibition of dopaminergic and alteration of cholinergic and GABAergic activity [116-118]. Indeed these hypotheses have been linked to SSRI-induced dystonic reactions. However, most of these hypotheses are not supported by direct experimental data in humans, nor specifically address OGCs.

Taken together, although the vast majority of conditions associated with OGCs are related with dopaminergic dysfunction, in the absence of direct experimental data, hypotheses regarding the origin of OGCs remain speculative.

Treatment

Treatment strategies are variable and depend on the aetiology of OGCs. In drug-induced OGCs the first step of management should include removing or, if not possible, reducing the dose of the offending agent [10, 119]. In acute cases, administration of anticholinergics, such as benztropine (e.g. 2mg intravenous) and biperiden (e.g. 5mg intramuscular) or antihistaminics, such as diphenhydramine can lead to symptom alleviation within minutes. If response is lacking drug administration should be repeated after 15-30 minutes [119-122]. To avoid re-occurrence of symptoms over the

ensuing time frame oral administration of anticholinergics for at least 4-7 days is recommended [119]. Oral administration of anticholinergics may be the most feasible approach for cases seen outside the emergency setting. In cases of persistent lack of response oral treatment with benzodiazepines such as clonazepam (e.g. 0.5-4 mg) might provide symptom relief [123]. In cases of tardive OGCs the aforementioned agents might be insufficient and long-term treatment with (atypical) neuroleptics such as clozapine might be required [124, 125]. However, it should be noted that treatment effects might be limited in tardive OGCs, as substances such as clozapine themselves may also cause OGCs [126-128].

Treatment of OGCs with L-dopa may also be successful in patients with parkinsonism including idiopathic Parkinson's disease with OGCs related to wearing off [57, 58]; but also in other conditions such as Kufor Rakeb disease [76], NIID [78] and PKAN-associated neurodegeneration [81]. Of note, administration of L-dopa has been reported to elicit OGCs in patients with parkinsonism as peak-dose phenomenon and hence some caution is advised [47]. Although L-dopa is beneficial in postencephalitic parkinsonism, the presence of drug-induced dyskinesias in these patients limits therapeutic success [14]. Benztropine has also been reported to alleviate symptoms in patients with EL-like illness [95].

In OGCs associated with focal brain lesions (e.g. striatocapsular infarction [105], pallidonigral lesion [6], lentiform nuclei [107]) the use of anticholinergics has been reported beneficial. Single cases have highlighted the use of antihistaminics (ondansetron-induced encephalopathy [108] and posterior leukoencephalopathy syndrome [109]) and carbamazepin [103] in treatment of OGCs episodes.

Conclusion and future directions

The spectrum of conditions associated with OGCs is wide and encompasses three main categories of disorders: 1. drug-induced disorders, 2. hereditary and sporadic movement disorders, 3. disorders related to focal brain lesions. The common basis of these disorders is a metabolic, anatomical or functional disruption of the nigrostriatal pathway, mainly of dopamine metabolism. Treatment should be causal where possible (i.e. removal of triggering factors; avoidance of further exposure). In the acute phase restoration of the imbalanced neurotransmitters using anticholinergics can provide rapid improvement. In-depth understanding of the pathophysiological mechanisms is lacking.

Indeed, the systematic analysis of the data presented here also revealed several knowledge gaps pertaining to clinical and pathophysiological aspects of OGCs. There is large heterogeneity in the clinical presentations of OGCs between patients and conditions, but this remains largely underexplored and, therefore, poorly understood. While attempts have been made to delineate differences between associated phenomena, such as psychiatric and autonomic symptoms in some of the conditions presenting with OGCs [11], this has been based on retrospective literature reviews and there are no studies systematically characterizing prospective pharmacogenetic and clinical features. Hence, to date, no predictors have been identified regarding which patients could be susceptible to developing OGCs, under which conditions and how severe their clinical manifestations might be. Also, there are no well-established treatment recommendations for patients who fail to respond to first-line drugs. Paucity of systematic clinical data makes it challenging to pinpoint concise pathophysiological mechanisms of OGCs. Indeed, although our systematic review provides evidence that both the dopaminergic and cholinergic system are involved in the pathophysiology of

OGCs, the exact mechanisms, including functional neuroanatomic and neuropharmacologic underpinnings, remain elusive. Animal models, alongside neuropathologic case studies, as well as in-vivo high-resolution structural and functional neuroimaging will be helpful to shed further light on these matters. Indeed, addressing the aforementioned questions will inevitably lead to better patient care. Importantly, it will also expand our understanding beyond the narrow pathophysiological framework of OGCs by providing information on the interplay between dystonic (oculomotor) symptoms with psychiatric and autonomic phenomena. The number of different etiological conditions with partially overlapping, but distinct pathophysiologies we provide here is a first step towards understanding the pathophysiology behind OGCs and their associations.

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