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A Brief Review on Clinical Treatment of Oculogyric Crisis

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ABSTRACT

As of now, there are increasing cases related to oculogyric crisis (OGC), mainly focusing on clinical manifestations. The pathogenesis of OGC is still uncertain, and there is no unified treatment protocol. This review aims to explore the treatment and management strategies for OGC based on existing cases, hoping to provide references for clinicians in identifying and treating OGC in practice.

Introduction

Oculogyric crisis (OGC) is a neurological disorder characterized by focal ocular muscle dystonia, which was first observed in patients with post-encephalitic parkinsonism between 1910 and 1930[1-2]. Studies report an incidence rate of OGC at approximately 5.3%[3]. OGC is mainly characterized by paroxysmal involuntary eye muscle spasms with fixed upward gaze, accompanied by anxiety, hallucinations or delusions, as well as other autonomic signs such as neck dystonia, tongue protrusion, dilated pupils, sweating, elevated blood pressure, tachycardia, facial flushing, drooling, and difficulty urinating, with each episode lasting from a few seconds to several hours. OGC is a form of extrapyramidal reaction dystonia-dyskinesia, classified as acute[1] and tardive[4], with the former being more common, occurring within minutes to hours, while the latter may sometimes occur weeks or months after an acute event. The diagnosis of OGC is mainly based on clinical symptoms, with careful history taking and physical examination to exclude the possibility of focal seizures, meningitis, encephalitis, head injury, parkinsonism, and other types of movement disorders.

Etiology and Pathogenesis

To date, the mechanism of OGC is still unclear, with most brain injuries leading to OGC existing in the nigrostriatal pathway[5]. The causes of OGC are diverse, including antipsychotics[6], antiemetics[7], antibiotics[8], antidepressants[9], antiepileptic drugs[10], and antimalarials[11] inducing OGC, while various genetic[12] or neurological metabolic diseases affecting dopamine production, storage, or reuptake can also be associated with OGC[13-14].

Like other acute drug-induced dystonias, OGC may be related to an imbalance between dopaminergic and cholinergic neurotransmission in the nigrostriatal pathway[1]. Clinical evidence supports this hypothesis, as anticholinergic drugs usually improve OGC symptoms. However, the imbalance between dopaminergic and cholinergic neurotransmission may not be the only pathophysiological explanation for all OGC cases. The pathophysiology of tardive OGC may be different and more complex, possibly related to chronic dopamine receptor blockade, neurodegeneration of striatal interneurons, and dysfunction of striatal

gamma-aminobutyric acid (GABA) interneurons leading to hypersensitivity of striatal dopamine receptors[15]. Most genetic and sporadic movement disorders associated with OGC (such as Parkinson's disease and Wilson's disease) have a direct relationship with anatomical disruption of dopamine synthesis[1]. Studies on patients with focal brain lesions (such as multiple sclerosis and encephalitis) showing OGC have found damage to the midbrain or basal ganglia where the nigrostriatal pathway is located[8].

In summary, although the common basis for most diseases associated with OGC is the metabolic, anatomical, or functional disruption of the nigrostriatal pathway, mainly dopamine metabolism, hypotheses about the origin of OGC remain speculative in the absence of direct experimental data. Therefore, dopaminergic neurotransmission seems to be at the center of the pathophysiology of OGC.

Risk Factors and Impact

The use of antipsychotic drugs is currently the most common cause of OGC[1]. OGC is more common in young people, males, those using high-potency typical antipsychotics, at high doses, and via parenteral administration[16]. Recent studies report that atypical antipsychotics (including olanzapine[6], quetiapine[17], lurasidone[18], risperidone[19], and aripiprazole[20], etc.) can also cause OGC, and patients with a family history of neurological diseases are also prone to OGC[12]. Although the occurrence of OGC symptoms is not fatal, it can reduce patient compliance, increase fatigue and sleep disorders, increase stigma leading to social avoidance, and affect daily activities such as driving, shaving, grooming, or dressing, ultimately causing significant psychological and physical impacts on patients[18]. Additionally, OGC is self-limiting and not easily observed by doctors, which increases the difficulty in identification and diagnosis. Therefore, it is important to understand their phenomenology and pathophysiology to achieve optimal clinical management and treatment[1].

Clinical Management and Treatment

Studies show that the treatment strategies for OGC are related to the cause[21]. In other words, timely diagnosis and early identification of the causative factors play a crucial role in the course and management of OGC.

Treatment of Drug-Induced OGC

For drug-induced OGC (such as antipsychotics), the dosage of the causative medication is usually gradually reduced. If OGC persists despite dosage reduction, it is recommended to discontinue the problematic drug. Antiemetics or antipsychotics can cause OGC by disrupting dopaminergic transmission[22], and for such patients, a reduction or cessation of medication can be adopted. A report on acute OGC caused by a third-generation cephalosporin antibiotic found that the patient's symptoms disappeared 48 hours after stopping the medication[8]. In cases of oculogyric crisis after the use of atypical antipsychotics, it was found that the symptoms of two patients improved by reducing the drug dose[16]. In another three cases of OGC caused by aripiprazole, the OGC symptoms of two patients were relieved by reducing the dose of aripiprazole, which also suggests that the clinical manifestations of OGC may be dose-dependent, while the symptoms of another patient persisted despite medication reduction or switching[23]. The latest reports have found that low-dose risperidone can also cause OGC[21], which may emphasize individual susceptibility (such as the assumed dopaminergic receptor density) as an important factor for the occurrence of OGC.

In acute cases, in addition to discontinuing the causative medication, immediate intravenous or intramuscular administration of anticholinergic drugs (benztropine and biperiden), or the use of antihistamines (intramuscular diphenhydramine or intravenous or intramuscular promethazine), or benzodiazepines (intravenous diazepam) can generally relieve OGC symptoms within minutes. If OGC symptoms do not resolve, the medication should be repeated after 15-30 minutes. To prevent the recurrence of OGC symptoms in subsequent time frames, it is recommended to continue oral anticholinergic medication for at least 4-7 days. For non-urgent cases, oral anticholinergic medication may be the most feasible approach. If the effect is unsatisfactory, oral benzodiazepines such as clonazepam may also help relieve OGC symptoms.

Research shows that the extraocular muscle dystonia in OGC is due to increased cholinergic input, and unopposed cholinergic stimulation can lead to excessive excitability of medium spiny neurons, causing dystonia[24]. Therefore, OGC responds to oral anticholinergic drugs. A serviceman using aripiprazole developed OCG, and symptoms quickly subsided after receiving diphenhydramine[25], which is consistent with the hypothesis of dopamine deficiency and relative cholinergic overactivity[26]. In a case of acute OGC caused by aripiprazole in 2023, it was found that all related symptoms were relieved once anticholinergic drugs were used to treat OGC and aripiprazole was discontinued[27]. Studies on ocular crises after the use of atypical antipsychotics found that symptoms improved after switching to a combination of risperidone and anticholinergic drugs[19]. A report on acute OGC caused by lurasidone found that OGC symptoms disappeared after treatment with anticholinergic drugs and clonazepam[18]. In addition to using anticholinergic drugs or antihistamines, oral or intravenous benzodiazepines (such as clonazepam) can also relieve OGC symptoms[28]. In cases of acute OGC caused by antiemetics, OGC symptoms were relieved

after using anticholinergic drugs, antihistamines, and benzodiazepines[29].

In addition to the above options, other antipsychotics with a lower likelihood of causing dystonic reactions, such as clozapine or quetiapine. Previous cases have found that patients with persistent ocular crises, obsessive thoughts, and psychiatric symptoms after long-term use of typical and atypical antipsychotics experienced improvement in OGC symptoms after switching to quetiapine[30]. In another case, the patient's OGC symptoms did not improve with the addition of anticholinergic medication but stabilized with clozapine[19]. It is worth noting that the therapeutic effect of tardive OGC may be limited, as clozapine itself can also cause OGC[26].

Treatment of OGC from Other Causes

In addition to drug-induced OGC, some case reports suggest that levodopa can improve OGCs in patients with parkinsonism, but more research is needed to verify the efficacy of this treatment[31]. Individual cases indicate that patients with OGC due to focal brain injury may benefit from anticholinergic or antihistamine treatment[8].

In conclusion, the treatment of drug-induced OGC mainly involves reducing or discontinuing the causative medication, followed by the addition of anticholinergic drugs, antihistamines, or benzodiazepines. For OGC caused by atypical antipsychotics, other medications with a lower likelihood of causing dystonic reactions, such as clozapine or quetiapine, can be considered. To avoid recurrence, it is recommended to continue treatment for OGC for at least a week. But patients with tardive OGC sometimes require longer treatment and observation periods[1]. OGC should be managed through a detailed medical history, examination, serial assessments, medication, and regular follow-up.

Conclusion

To diagnose and appropriately manage OGC in a timely manner, clinicians need to learn to identify the causes of OGC. The pathogenesis of OGC is not clear, and current treatment strategies mainly depend on the cause, with different treatment strategies for OGC caused by different causes.

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