An update on opsoclonus

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Purpose of review

The aim of this article is to review opsoclonus, with particular emphasis on its immunopathogenesis and pathophysiology.

Recent findings

Infections (West Nile virus, Lyme disease), neoplasms (non-Hodgkin's lymphoma, renal adenocarcinoma), celiac disease, and allogeneic hematopoietic stem cell transplantation can cause opsoclonus. Newly identified autoantibodies include antineuroleukin, antigliadin, antiendomysial, and anti-CV2. Evidence suggests that the autoantigens of opsoclonus reside in postsynaptic density, or on the cell surface of neurons or neuroblastoma cells (where they exert antiproliferative and proapoptotic effects). Most patients, however, are seronegative for autoantibodies. Cell-mediated immunity may also play a role, with B and T-cell recruitment in the cerebrospinal fluid linked to neurological signs. Rituximab, an anti-CD20 monoclonal antibody, seems efficacious as an adjunctive therapy. Although changes in synaptic weighting of saccadic burst neuron circuits in the brainstem have been implicated, disinhibition of the fastigial nucleus in the cerebellum, or damage to afferent projections to the fastigial nucleus, is a more plausible pathophysiologic mechanism which is supported by functional magnetic resonance imaging findings in patients.

Summary

There is increasing recognition that both humoral and cell mediated immune mechanisms are involved in the pathogenesis of opsoclonus. Further studies are needed to further elucidate its immunopathogenesis and pathophysiology in order to develop novel and efficacious therapy.

Keywords

antineuronal antibodies, autoimmunity, fastigial nucleus, neuroblastoma, opsoclonus, paraneoplastic syndrome

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Abbreviations

ACTH	adrenocorticotropic hormone
CSF	cerebrospinal fluid
IVIG	intravenous immunoglobulin
MRI	magnetic resonance imaging

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Introduction

Opsoclonus is a dyskinesia consisting of involuntary, arrhythmic, chaotic, multidirectional saccades, without intersaccadic intervals [1–3]. The etiology of opsoclonus is varied, and includes paraneoplastic, parainfectious, toxic–metabolic, or idiopathic causes. Humoral and cell mediated immune mechanisms have both been implicated. Although a number of autoantibodies have been detected, the majority of patients with opsoclonus are seronegative for all known antineuronal antibodies. Investigations are directed toward detecting any underlying tumors, and excluding other causes. This review summarizes the clinical features, etiology, investigation, treatment, as well as the course and prognosis of opsoclonus, with particular focus on recent advances in our understanding of its immunopathogenesis and pathophysiology.

Clinical features

Opsoclonus consists of involuntary, arrhythmic, chaotic, multidirectional saccades, with horizontal, vertical, and torsional components [1–3]. It is present during fixation, smooth pursuit, convergence, and persists during sleep or eyelid closure. Because of its large amplitude and high frequency (10–15 Hz), it frequently causes visual blur and oscillopsia (an illusion of movement of the seen world). Opsoclonus differs from nystagmus in that the phase that takes the eye off the target is always a saccade, not a slow eye movement. In contrast to ocular flutter, which consists of back-to-back saccades that are confined to the horizontal plane, opsoclonus is multidirectional [1–4]. Opsoclonus is often accompanied by myoclonic jerks of the limbs and trunk, hence the term 'opsoclonus–myoclonus' or 'dancing eye and dancing feet syndrome'. Cerebellar ataxia, postural tremor, encephalopathy, and behavioral disturbances are also frequently associated.

Etiology

Opsoclonus can occur in many clinical settings (Table 1 [5–59]), including paraneoplastic syndromes, parainfectious brainstem encephalitis, and toxic–metabolic states.

Table 1 Etiology of opsoclonus and ocular flutter

	References
Paraneoplastic effect of neuroblastoma and other neural crest tumors (in children)	[5,6]
Paraneoplastic effect of other tumors (in adults)	[7–15]
Parainfectious encephalitis	[1,16–27,28••,29]
Multiple sclerosis	[4,30–32]
Meningitis	[33]
Intracranial tumors	[34]
Hydrocephalus	[35]
Thalamic hemorrhage	[36]
In association with systemic disease	
AIDS	[37,38,39••]
Celiac disease	[40••]
Viral hepatitis	[41]
Sarcoid	[42]
Following allogeneic hematopoietic stem cell transplantation	[43]
Hyperosmolar coma	[44,45]
Toxins	
Chlordecone	[46]
Organophosphates	[47]
Strychnine	[48]
Thallium	[49]
Toluene	[50]
Side effects of drugs	
Amitriptyline	[51]
Cocaine	[52]
Lithium	[53,54]
Phenytoin with diazepam	[55]
Phenelzine with imipramine	[56]
As a complication of pregnancy	[57]
As a transient phenomenon of normal infants	[58,59]

Not all case reports have eye movement recordings.

In many cases, however, no obvious cause is found (i.e. idiopathic opsoclonus). In paraneoplastic opsoclonus, small cell lung, breast, and ovarian cancer are most commonly encountered in adults [1,60], whereas more than half of cases are associated with neuroblastoma in children. Diseases that have recently been reported to cause opsoclonus include infections such as West Nile virus [29], streptococcal infection [28••], varicella-zoster infection [25], and Lyme disease [27]; neoplasms such as non-Hodgkin's lymphoma [13], malignant melanoma [14], and renal adenocarcinoma [15]; and celiac disease [40••]. A case of opsoclonus following allogeneic hematopoietic stem cell transplantation has also been reported [43].

Immunopathogenesis

Humoral and cell mediated immune mechanisms have both been implicated in paraneoplastic and idiopathic opsoclonus [61]. In support of a humoral immune mechanism, paraneoplastic opsoclonus has been associated with a number of autoantibodies. They include anti-Ri (ANNA-2) [62], anti-Yo (PCA-1) [63], anti-Hu (ANNA-1) [64], anti-Ma1 [65], anti-Ma2 [3], anti-amphiphysin [66,67], anti-CRMP-5/anti-CV2 [40••,68], anti-Zic2 [69], and antineurofilaments [70]. New autoantibodies identified in two recent case reports include antineuroleukin antibodies in two girls with poststreptococcal opsoclonus–myoclonus syndrome [28••], as well as antigliadin antibodies of immunoglobulin A subtype, antiendomysial antibodies, and anti-CV2 antibodies in a child with celiac disease [40••].

Because of the frequent reversibility of symptoms, especially after immunotherapy, and the paucity of findings on pathological examination, it has been suggested that the putative autoantigens reside on the cell surface or in the synapse, and that the antibodies cause transient neuronal dysfunction rather than permanent neuronal degeneration [67]. Recently, Blaes *et al.* [71••] detected autoantibodies binding to cell surface of cerebellar granular neurons. In another study, Bataller *et al.* [69] probed a brainstem cDNA library to isolate target neuronal antigens by using sera of 21 patients with idiopathic or paraneoplastic opsoclonus. They [69] found two groups of autoantigens: (1) proteins of the postsynaptic density (PSD), a complex of proteins associated with the glutamate *N*-methyl-D-aspartate (NMDA) receptor that includes membrane proteins (such as receptors, ion channels, and adhesion molecules) attached to a network of intracellular scaffold, signaling and cytoskeletal proteins; and (2) proteins with expression or function restricted to neurons, including RNA or DNA-binding proteins and zinc-finger proteins.

Despite progress in identifying autoantibodies, the majority of patients with opsoclonus are seronegative for all known antineuronal antibodies. In addition, there are no definitive links between various autoantibodies and neurological abnormalities [72]. These observations suggest that a cell mediated immune mechanism may play a role in the pathogenesis of opsoclonus. Three recent studies lend further support to a cell mediated immune mechanism. (1) Pranzatelli *et al.* [73] found that although most children with opsoclonus have normal cell counts in the cerebrospinal fluid (CSF), they have expansion of CD19+ B-cell (up to 29%) and $\gamma\Delta$ T-cell (up to 26%) subsets with a reduced proportion of CD4+ T-cells and reduced CD4/CD8 ratio. These abnormalities persist for years after disease onset despite treatment, and they correlate with neurologic severity as well as disease duration. (2) Opsoclonus responds to treatment with rituximab, an anti-CD20 monoclonal antibody, with clinical improvement correlating with B-cell reduction in the CSF [74•,75••]. (3) van Toorn *et al.* [39••] reported an HIV-infected child who developed opsoclonus–myoclonus shortly after commencement of highly active antiretroviral therapy, and postulated that T-cell recovery and recruitment following rapid immune reconstitution may have resulted in immune reconstitution-induced opsoclonus–myoclonus.

Interestingly, the prognosis for survival of neuroblastoma patients with opsoclonus is better than for those without opsoclonus [76]. In addition, neuroblastoma has a high

incidence of spontaneous regression. These observations, together with the suspected autoimmune pathogenesis, suggest that opsoclonus may represent an effective anti-tumor immunity that protects against tumor growth and dissemination. Recently, Korfei *et al*. [77••] demonstrated that IgG autoantibodies from neuroblastoma patients with opsoclonus, but not those from neuroblastoma patients without opsoclonus, bind to surface autoantigens on neuroblastoma cells, and that these autoantibodies inhibit cell proliferation and induce apoptosis in neuroblastoma cells.

Pathophysiology

The pathophysiology of opsoclonus is uncertain. Burst neurons in the paramedian pontine reticular formation (PPRF) and rostral interstitial nucleus of Cajal (riMLF) are responsible for generating the immediate premotor command for saccades. Omnipause cells in the pontine nucleus raphe interpositus (rip) normally inhibit these burst neurons, preventing unwanted saccades. Thus, damage to omnipause cells might cause opsoclonus [78]. Lesions of omnipause cells, however, cause slowing of saccades, not saccadic oscillations [79,80]. In addition, on autopsy, no histopathologic changes in omnipause cells were found in most patients with opsoclonus [3,81].

Cerebellar dysfunction has also been invoked in the pathogenesis of opsoclonus in view of damage to Purkinje cells, granular cells and the dentate nuclei in patients with opsoclonus [82–84]. These cerebellar changes also occur, however, in patients with paraneoplastic cerebellar degeneration who do not have opsoclonus. Moreover, partial ablations of the cerebellar cortex [85] or cerebellectomy including the deep nuclei [85,86] have not been observed to cause opsoclonus in monkeys. Inactivation of the caudal fastigial nucleus of the cerebellum produces saccadic overshoot dysmetria with intervals between sequential saccades, not opsoclonus [87,88].

Currently, two hypothetical models seem plausible. One hypothesis [89••] suggests that saccadic oscillations arise because of the synaptic organization of burst neurons in the brainstem, in which positive feedback loops and postinhibitory rebound properties of burst neurons predispose to saccadic oscillations. Changes in the synaptic weighting of saccadic burst neuron circuits in the brainstem due to disease may produce oscillations (such as microflutter) whenever the omnipause cells are inhibited [89••,90]. The amplitude of the saccadic oscillations generated by this model, however, is much smaller (10–20 times) than the large amplitude oscillations that are typically seen in opsoclonus. In addition, the biophysical mechanism underlying the purported change in synaptic organization of burst neurons is unclear, and clinical correlation is lacking.

Another more plausible hypothesis [3] proposes that disinhibition (not inactivation) of the fastigial nucleus in the cerebellum causes opsoclonus. Malfunction of Purkinje cells in the dorsal vermis or their inhibitory projections to the fastigial nucleus may cause opsoclonus by disinhibiting the fastigial nucleus [3]. Four lines of evidence support this hypothesis. (1) Histopathological examination of a patient with opsoclonus revealed damage to afferent projections to the fastigial nucleus [3]. (2) Long-term potentiation of slow inhibitory postsynaptic current, but not excitatory postsynaptic current, is abolished in mice lacking Nova-2, a neuronal-specific RNA binding protein that is an autoimmune target in patients with paraneoplastic opsoclonus [91••]. Nova-2 normally contributes to inhibitory synaptic transmission or synaptic plasticity, or both. Defective Nova-2 may be responsible for reduced inhibitory control (i.e. disinhibition) of movements seen in opsoclonus–myoclonus syndrome. (3) In two patients with opsoclonus, single photon emission computed tomography identified the area of dysfunction to the cerebellar vermis, where Purkinje cells normally exert inhibitory control over the fastigial nucleus [39••,92]. (4) Perhaps the most convincing evidence comes from a functional magnetic resonance imaging (MRI) study that demonstrated bilateral activation (i.e. disinhibition) of the fastigial nucleus in two patients with opsoclonus. Furthermore, this pattern of cerebellar activation is not observed in healthy controls during high-frequency saccades [93].

Investigation

A thorough diagnostic evaluation for the presence of tumor is necessary for all patients with opsoclonus, after exclusion of central nervous system pathology and lumbar puncture. In most cases, brain MRI is normal, and CSF analysis may show mild pleocytosis and protein elevation. At the present time, commercial tests for antibodies are of limited diagnostic value because most patients with opsoclonus are seronegative for autoantibodies.

In children, a search for occult neuroblastoma is essential. Investigations should include imaging of chest and abdomen (computed tomography scan or MRI), urine catecholamine measurements, including vanillyl mandelic acid and homovanillic acid, as well as ^{123}I-metaiodobenzylguanidine scan [94]. When negative, the evaluation should be repeated after several months [95].

In adults, initial investigations for paraneoplastic opsoclonus should be directed at tumors associated with this condition. They include high resolution computed tomography of the chest and abdomen, as well as gynecological examination and mammography in women [67]. When negative, whole body ^{18}F-fluoro-2-deoxyglucose-positron emission tomography scan should be considered [96,97].

Treatment

Treatment of the underlying process such as tumor or encephalitis is the mainstay of management for opsoclonus [67]. To date, however, no data are available from prospective controlled trials with regard to treatment strategies and their correlation with long-term outcome in patients with opsoclonus.

In children, corticosteroids, intravenous immunoglobulin (IVIG), and adrenocorticotropic hormone (ACTH) are the most common immunomodulatory agents used for paraneoplastic opsoclonus. In many centers, children are treated with prednisone (2 mg/kg/day) and monthly IVIG (2 g/kg at induction, followed by a monthly maintenance dose of 1 g/kg [75••,98]). If symptoms improve, prednisone is slowly tapered starting at 2–3 months over a 9–12-month period. If relapse or exacerbation occurs (not due to recurrence of neuroblastoma), the dosage of prednisone, and sometimes IVIG, are increased. For symptoms that remain difficult to control despite the above therapy, a low dose cyclophosphamide (1–5 mg/kg) is often added. Currently, the Children's Oncology Group at the National Cancer Institute (NCI) of the USA is conducting a randomized, multicenter clinical trial to determine whether cyclophosphamide and prednisone with or without IVIG is a reasonable baseline standard therapy for pediatric patients with neuroblastoma-associated opsoclonus–myoclonus–ataxia syndrome.

ACTH is also used in many centers for pediatric opsoclonus–myoclonus syndrome [75••]. A 40-week protocol has been used: H.P. Acthar Gel (80 IU/cm^3; Questcor, Union City, California, USA) is injected intramuscularly at an initiation dose of 75 IU/m^2 twice a day for one week, daily for one week, every other day for 2 weeks, then gradually dropping to 40 IU/m^2 over 2 months, when the rate of taper decelerates to 5 IU/m^2 every month until a final dose of 5 IU/m^2 is reached [75••]. If relapse occurs, the tapering is halted, and the previous dose that controls the symptoms is resumed. Recently, Pranzatelli *et al.* [99••] demonstrated that daily high-dose ACTH treatment dramatically raises the concentration of cortisol in CSF, but alternate day and low-dose ACTH do not. They [99••] suggested that elevated level of cortisol in the brain may make ACTH more efficacious than oral corticosteroids in inducing a neurologic remission. Because ACTH, like corticosteroids, exerts many neurotropic [100] and immunologic effects [61], however, the relative contribution of elevated level of cortisol in the brain cortisol remains uncertain. Prospective dose–response and time course studies are needed to further clarify the therapeutic effects of ACTH.

Plasmapheresis may be useful in refractory cases that do not respond to ACTH or corticosteroids. In a patient with ganglioneuroblastoma and delayed, recurrent opsoclonus 9 years after completing treatment, combination therapy with plasmapheresis and corticosteroids results in symptom resolution for 3 years [101]. Rituximab (375 mg/m^2 of body surface area intravenously once weekly for four consecutive weeks), an anti-CD20 monoclonal antibody, has also recently been shown to be efficacious and safe as adjunctive therapy [74•,75••,102,103].

In adult-onset idiopathic opsoclonus–myoclonus, corticosteroids or IVIG seem to accelerate recovery [67]. In contrast to pediatric neuroblastoma-associated opsoclonus, no clear advantage of immune therapy has been demonstrated in adults with paraneoplastic opsoclonus [67]. Improvement following the administration of corticosteroids, cyclophosphamide, azathioprine, IVIG, plasma exchange, or plasma filtration with a protein A column has been described in single cases [104–108].

Symptomatic therapy of nystagmus and oscillopsia includes the use of propranolol (40–80 mg orally three times daily), nitrazepam (15–30 mg orally daily), baclofen, clonazepam (0.5–2.0 mg orally three times daily), and thiamine (200 mg intravenously) [109–111]. Myoclonus can be treated with antiepileptic drugs.

Course and prognosis

In children, the course of opsoclonus–myoclonus is characterized by multiple relapses, which require prolonged treatment, and significant developmental sequelae [112••]. Only a minority of children has a monophasic course and a more benign prognosis [112••]. In children with neuroblastoma and opsoclonus, the opsoclonus usually resolves eventually with or without treatment. Residual opsoclonus may reappear after apparent complete resolution when medication is reduced, or during intercurrent illnesses [113]. Developmental sequelae are common, and include motor, speech, and language deficits. Psychiatric symptoms, such as aggressive and disruptive behavior, impulsivity, affective dysregulation, irritability, cognitive impairment, poor attention, and sleep disturbances may persist [114•]. Immunosuppressive agents may improve behavioral symptoms and motor functions; but psychotropic medications may be necessary in selected children who have severe behavioral or sleep disturbances [113]. Trazodone (3.0 ± 0.4 mg/kg/day), a soporific serotonergic agent, was recently reported to be effective in improving sleep and decreasing rage attacks, and it is well tolerated, even in toddlers [115•].

In adults, the clinical course of idiopathic opsoclonus is monophasic with good recovery in the majority of patients; in older patients, however, relapses of opsoclonus may occur and residual gait ataxia tends to persist. Immunotherapy (corticosteroids or IVIG) seems to accelerate recovery. In contrast, paraneoplastic opsoclonus has a more severe course, despite treatment with

corticosteroids or IVIG, and mortality rate is high in patients whose tumors are not treated. Most patients who undergo treatment for the underlying tumors have complete or partial neurological recovery [67].

Conclusion

The exact immunopathogenesis of opsoclonus is uncertain. There is increasing recognition, however, that both humoral and cell mediated immune mechanisms are involved. Although changes in the synaptic weighting of saccadic burst neuron circuits in the brainstem may produce saccadic oscillations, clinical correlation is lacking. Further experiments, such as selective blockades of individual channels or intracellular recordings, are needed to investigate the biophysical characteristics of burst neurons and the purported change in synaptic organization. At the present time, disinhibition of the fastigial nucleus in the cerebellum, or damage to afferent projections to the fastigial nucleus, is a more plausible pathophysiologic mechanism which is supported by a degree of evidence, including functional MRI findings in affected patients. Because previously normal individuals are rapidly disabled neurologically by opsoclonus–myoclonus syndrome, and because available treatments are often less than satisfactory, a better understanding of the immunopathogenesis and pathophysiology of opsoclonus is essential to develop and identify novel treatment modalities.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 84).

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