Review

The Immunopharmacology of the Opsoclonus–Myoclonus Syndrome

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Summary: The opsoclonus–myoclonus syndrome (OMS) is a potentially devastating paraneoplastic or paraviral syndrome. Although it is a rare disorder, it has major implications for cancer, virology, immunology, developmental neurobiology, and molecular pharmacology. The mechanism of brain injury in OMS is unknown, but evidence suggests immune system dysregulation. This article surveys recent clinical and laboratory evidence for the autoimmune theory and discusses how some current therapies for OMS may exert their effects through immunomodulation. Specific testable hypotheses on the immunologic defect in OMS involving both B cells and T cells, the nature and mechanisms of brain injury, and their clinical correlations are proffered. The current therapeutic armamentarium provides a broad spectrum of nonselective immunotherapies, including noncytotoxic and cytotoxic drugs, intravenous immunoglobulins, and plasma exchange, some selected for induction and others for maintenance. The use of combination immunotherapies may allow steroid sparing, targeting of more than one immunologic effector pathway, and a mixture of early- and late-acting drugs. More selective immunotherapies, now available or in preclinical and clinical trials, have great potential for the treatment of OMS but require precise information on the underlying immunological problem. These data provide possible new directions for immunologic research and therapy in OMS. **Key Words:** Myoclonus—Opsoclonus—Intravenous immunoglobulins—ACTH—Neuroblastoma—Plasmapheresis—Paraneoplastic syndromes—Immunomodulation—Autoimmunity.

So little is known about the immunobiology of the opsoclonus–myoclonus syndrome (OMS), it may be presumptuous to attempt to review it. Yet the problem is urgent: previously normal individuals are rapidly disabled neurologically by a

putative immunologic disorder with few good treatment options. The neurobiology of OMS, including clinical and laboratory features, has been reviewed recently (1). Briefly, the clinical features of the syndrome have long been known to include opsoclonus, myoclonus, ataxia, dysarthria, behavioral and cognitive problems in children, and other encephalopathic features in adults. The etiologic association of OMS with a remote neoplasm (paraneoplastic) or a nonencephalitic viral infection (paraviral) (2,3), each attributed to nearly half of the cases, is more common than rare cases caused by other acquired and genetic disorders. An immunogenic mechanism of OMS was suggested almost 20 years ago (4) and recently has been gaining support. The fact that both a reaction to a tumor and to a virus could induce the same clinical syndrome in both infants and adults has presented both a puzzle and a clue. This review proposes to explore both the immunologic puzzle and the clue, recent clinical and laboratory data, a large body of knowledge about immunoregulation and autoimmunity, and old and new treatments in search of pathophysiologic explanations and the mechanism of action of current therapy. The goal is to construct testable hypotheses, provide a rational basis for the use of new therapies, and stimulate further research in this area.

EVIDENCE FOR AN IMMUNOLOGIC MECHANISM

Criteria for Opsoclonus–Myoclonus as an Autoimmune Disorder

There are five classical strict criteria for an autoimmune disease (5). A defined circulating antibody or cell-mediated immunity to autoantigens is required, but most patients with OMS do not exhibit detectable levels of suspect circulating antibodies. The second criterion is the definition of the specific autoantigen: given that both peripheral neoplasms and various viruses are the typical etiologies of OMS, an apparent common denominator is unknown. The next three criteria require an animal model, which is lacking in OMS. First, the disease must be produced in an experimental animal by passive transfer of the antibody or the self-reacting cells. The disease then must be produced by immunization with the self-antigen in the presence of complete Freund's adjuvant. Last, such an immunization must be able to generate the autoantibodies or the self-reacting cell. Like most other putative autoimmune disorders, OMS would not meet these criteria. However, circumstantial evidence supports an autoimmune basis for OMS.

Immunopathology

Many observations support an immunologic mechanism in the pathophysiology of OMS, some more directly than others (Table 1). More is known about paraneoplastic than paraviral OMS, and most of the information comes from the adult-onset OMS. Because there are differences between OMS in children and adults, they are discussed separately.

OMS in Adults

Tumors associated with adult-onset paraneoplastic OMS are peripheral to the CNS in all but one reported case (6). Immunologic abnormalities occur in cancer

TABLE 1. *Evidence supporting an immunologic mechanism in opsoclonus-myoclonus*

Observation	Reference
Neuroblastoma without paraneoplastic syndrome	
Natural history of spontaneous regression of neuroblastoma	22
Lymphocytic infiltrates in tumors from patients with a good prognosis	24
Lymphocytes cytotoxic to neuroblastoma from affected patients in vitro	25, 27
Presence of "blocking antibodies" to lethal effects of lymphocytes against neuroblastoma in vitro is prognostically unfavorable	26
Less consistent cytotoxic effect on neuroblastoma of plasma from patients	28
Occurrence of myasthenia gravis as a presentation of neuroblastoma	30
Opsoclonus-myoclonus	
Tumors are peripheral to the CNS, not intracranial	3, 35
Neurologic improvement in some patients after tumor resection or chemotherapy	3
Response to ACTH or steroids	2
Quantitative serum IgG abnormalities and CSF plasmacytosis	38, 39
Better prognosis for survival of patients with paraneoplastic syndrome	33
Cooccurrence of paraneoplastic opsoclonus-myoclonus and myasthenia gravis	30, 31
Circulating antineurofilament antibodies	90
Circulating cerebellum-specific immunoreactivity	56–59
Paraneoplastic autoantibodies (anti-Hu and anti-Ri)	63, 81
Abnormal reactivity to neuroblastoma extract in leukocytes from pediatric opsoclonus	34
Decreased suppressor T-lymphocyte function in an adult with opsoclonus and breast cancer	94
Lymphocytic infiltrate in the tumors of patients with opsoclonus-myoclonus	
Other associations	
Autoantibodies to neuroblastoma in neuropsychiatric lupus	32

CNS, central nervous system; ACTH, adrenocorticotropic hormone; IgG, immunoglobulin G; CSF, cerebrospinal fluid.

patients in the presence or absence of a paraneoplastic syndrome (7–9). In adults, the tumor may be so small as to escape detection and be found only at autopsy (10). CSF immunoglobulin abnormalities have been reported in OMS in adults (11–14) with intrathecal antibody (immunoglobulin G; IgG) synthesis (15,16).

The neuropathology of OMS has not been studied using modern techniques but provides some immunologic clues. Loss of both cerebellar Purkinje and granule cells with gliosis (in one case with lymphocytic infiltrations) or groups of Purkinje cells alone, or lesions of the inferior olives, lower medulla, or upper cervical cord have been found (17–20). Inflammatory infiltrates of T cells and B cells have been reported (21). Neuropathologic findings in an idiopathic (viral) case of OMS were very similar to those described in paraneoplastic cerebellar cortical degeneration (18), despite differences in the phenotype of the two syndromes. In many of the paraneoplastic cases, the influence of systemic illness, chemotherapy, and agonal postmortem changes in brain must be considered in interpreting these neuropathologic findings.

OMS in Children

Even in children with neuroblastoma without a paraneoplastic syndrome, several lines of evidence suggest heightened immune responses to neuroblastoma. Neuroblastoma, the most common extracranial solid tumor in children, is asso-

ciated with the highest incidence of spontaneous regression of any solid tumor, found incidentally on infantile autopsy at an incidence 40 times greater than the clinical occurrence of neuroblastoma in childhood (22,23). Although both host and tumor factors could be implicated in this phenomenon, an immunologic mechanism is supported by the finding that lymphocytes infiltrate tumors from patients with a good prognosis (24), and blood lymphocytes are cytotoxic to neuroblastoma cells in culture (25–28). Survival from mediastinal neuroblastoma, the most common site in paraneoplastic OMS in children, is favorable even in the absence of a paraneoplastic syndrome (29). The immunologic disorder myasthenia gravis and neuroblastoma without OMS are rare co-occurrences (30), and myasthenia gravis with elevated antiacetylcholine receptor and antithyroglobulin antibodies was also reported in a 13-month-old girl who had OMS but no malignancy (31). Antibodies to neuroblastoma have been found in patients with neuropsychiatric lupus (32).

The fact that tumors associated with paraneoplastic OMS are found outside the central nervous system (CNS) also is compatible with an immunological remote mechanism. In children with the paraneoplastic syndrome, survival from the tumor is much better than in patients without the syndrome, and metastatic disease is rare (33). Lymphocytic tumor infiltrates and blood lymphocytes cytotoxic to neuroblastoma have been found in OMS (34).

In cases associated with a viral infection, there is no evidence of direct viral invasion of the brain; the virus is not directly encephalogenic. Clinically, the onset of symptoms usually follows a viral prodrome by several days, suggesting a para- or postviral process. Brain imaging is usually normal, even during the acute phase of the illness. Because neuroblastoma may induce OMS and then undergo spontaneous regression before clinical detection, it has been suggested that occult tumors are the cause of OMS in all cases (35). However, both DNA and RNA viruses, such as Epstein–Barr virus, St. Louis encephalitis, coxsackie B3, and mumps have been identified with the viral prodrome (14,36,37).

Immunologic abnormalities have been found in cerebrospinal fluid (CSF). CSF or serum IgG and IgM are increased in some cases of opsoclonus (38–41). CSF oligoclonal bands, which are not specific but are indicative of an inflammatory nervous system disorder (42), have also been found (41,43). The presence of interferon in the CSF was reported in one child with OMS (44).

Unlike adults, few children die from OMS, and pathologic studies are limited. Before OMS became a recognized syndrome, a frontal cortical biopsy was performed in a severe case, which was normal (2). Biopsy of the cerebellar vermis in a child with OMS, whose neuroradiologic studies had indicated a lesion, revealed Purkinje and granular cell loss with gliosis (20). In an autopsy of a 6-year-old with OMS due to metastatic ganglioneuroblastoma treated with chemotherapy, similar changes were found in the cerebellum (45). Autopsy of a 3-year-old girl with OMS, ganglioneuroblastoma-associated Cushing's syndrome, and a cerebellar subcortical lesion (vermis and hemisphere) on magnetic resonance imaging (MRI) scan confirmed cerebellar lesions and suggested regenerative gliosis (46). Reactive cells were positive for monocyte–macrophage antigens by immunohistochemistry, but there were no infiltrations of B or T lymphocytes.

Differences between Pediatric- and Adult-Onset OMS

Differences between OMS in children and adults have implications for the immunopathology (Table 2). The absence of microcephaly in most children together with normal MRI of brain suggests no widespread cell loss, edema, or inflammation. In adults with paraneoplastic cerebellar degeneration, necrosis, and atrophy, the situation is different (47). The paraneoplastic syndrome in adults, unlike that in children, may be progressive and lethal due to respiratory failure and dysautonomia. The range of neurologic paraneoplastic syndromes in adults also includes sensory neuronopathy–encephalomyelitis, brainstem encephalitis, optic neuritis, and retinal photoreceptor degeneration (10,48–50), which is different from paraneoplastic syndromes in children, about which less has been written (51,52). The developmental impact of OMS (53) is a phenomenon by definition relevant only to childhood-onset OMS.

Humoral Immunity

Several different types of circulating autoantibodies have been detected in patients with paraneoplastic syndromes with or without OMS (Table 3), and some autoantibodies also have been found in patients with no discernable tumor. These are associations in the absence of established causality; however, the presence of "paraneoplastic" autoantibodies should prompt a thorough search for an underlying neoplasm. The absence of autoantibodies does not rule out a neuroimmunologic disorder, because the same clinical phenotype may be present in patients with or without autoantibodies, as in stiff-man syndrome (54) or Sydenham's chorea (55).

OMS in Adults

Differences in the nomenclature of paraneoplastic antibodies are at times confusing and have led to uncertainty as to the exact relation of antibodies described

TABLE 2. *Key features of OMS for construction of model*

Similarities between children and adults
Discrete neurologic signs and symptoms
Clinical heterogeneity in phenotype
Etiologically a syndrome, not a disease
Tumors and viruses are outside the CNS
Immunologic mechanism
Subcortical ± cortical brain injury
Pediatric differences
Fixed insult, not progressive
Normal routine neuroimaging, usually
Cognitive developmental impact
May be more steroid responsive
Circulating paraneoplastic autoantibodies seldom found

OMS, opsoclonus–myoclonus syndrome; CNS, central nervous system.

TABLE 3. *Autoantibodies found in OMS*

Antibody	Antigen MW (kDa)[a]	Antigen	Tumor	Neurologic syndrome	Reference
Anti-NF	210	Neurofilament	Neuroblastoma	Opsoclonus–myoclonus	90
Anti-Hu[b]	35–40	Human analog of Drosophila elav protein	Small-cell lung cancer; neuroblastoma	Brainstem or limbic encephalitis	79
				Sensory or autonomic neuropathy	85
				Transverse myelopathy or motor neuron disease	
				Opsoclonus–myoclonus	
Anti-Ri[c]	55, 80	hnRNP K, MER 1	Gynecological cancers; breast cancer; small-cell lung	Opsoclonus	63
				Ataxia without opsoclonus	62
				Opsoclonus–myoclonus	86

OMS, opsoclonus–myoclonus syndrome.
[a] Antigen reaction in Western blot analysis.
[b] May overlap with the ANNA-1 and type IIa classifications.
[c] May overlap with the ANNA-2 and type IIb classifications.

by different laboratories. The classification of neurologic paraneoplastic antibodies has been based on the pattern of immunostaining alone (56) or the combination of immunohistochemistry and Western blotting (57). In one system, the terms ANNA (anti-neuronal nuclear antibody) and PCAb (anti-Purkinje cell cytoplasmic antibody), with numerical subdivisions, is used (56). A similar system divides anti-neuronal antibodies into type I (similar to PCA-1) and type IIa (like ANNA-1) and type IIb (like ANNA-2) (58,59). Another system names the antibodies for the antigens (57). Anti-Hu and anti-Ri antibodies are anti-nuclear and anti-neuronal and therefore may be analogous to ANNA-1 and ANNA-2, respectively, and also to type IIa and type IIb, respectively, but the terms apparently cannot be used synonymously (57). The history of and further distinctions between these approaches have been reviewed recently (57) and are not covered here.

The type of autoantibody may suggest a specific tumor (60). Anti-Hu has been associated with small-cell lung cancer (61), anti-Ri with breast cancer (62,63), and anti-Yo with gynecological cancers (64–67). All of the autoantibodies are antineuronal; many are anticerebellar (anti-Purkinje cell) but also react with neurons from cerebral cortex, and some also react with peripheral nerve (68–74). Reactivity to human neuroblastoma cells (SK-N-SH) has been reported recently (75). Tumors from adults with paraneoplastic cerebellar degeneration express Purkinje cell antigens (65). In adults, it has been proposed that different phenotypes of paraneoplastic disorders can be attributed to different autoantibodies. Phenotypes include cerebellar syndrome with degeneration, OMS, and various other neurologic signs such as peripheral or autonomic neuropathy. Anti-CAR has been implicated in paraneoplastic retinal degeneration (76–78).

Only the anti-Hu and anti-Ri antibodies are known to be relevant to OMS. The anti-Hu autoantibody reacts with neurons of the central and peripheral nervous system. Anti-Hu antibody in low titers is found in 10–15% of patients with small-cell lung cancer without a paraneoplastic disorder (79). One adult with anti-Hu–associated OMS has been reported (80). Anti-Ri antibodies were found in an adult with no detectable neoplasm in >3 years of follow-up, and high serum and CSF antibody titers persisted during recovery and a normal neurological examination (81). Anti-Ri also may be associated with a nonopsoclonic paraneoplastic syndrome (82). Also curious is the observation that the same tumor type, such as small-cell carcinoma of the lung, may also give rise to a different paraneoplastic syndrome, such as Eaton–Lambert syndrome, which 65% of the time is due to this tumor (83).

The various antigens for these antibodies are found in the CNS. The Hu family of mammalian proteins (HuC, HuD, Hel-N1) are expressed in nuclei of differentiating and mature neurons and also in neuroblastoma, adrenal medullary chromaffin cells, and bronchial cells (84). Hu proteins are important to the development and maintenance of neurons, encoded by related genes, and may function as regulatory RNA-binding proteins (85). The Hu protein has been cloned, and monoclonal antibodies (MoAb 16A11) have been raised against the recombinant Hu protein. Nova, a gene that encodes an antigen recognized by the anti-Ri antibody, is expressed in ventral brainstem and spinal cord in embryonic E18 mice (86). Nova-encoded proteins may be involved in signal transduction in neurons

and tumor cells (86). Yo antigens are encoded by genes mapped to the X chromosome and chromosome 16 (87).

OMS in Children

Anti-Hu antibodies are seldom found in the blood of children with OMS with or without neuroblastoma, in the experience of the National Pediatric Myoclonus Center (unpublished), and anti-Ri has not been reported in children. Anti-Hu antibody has been reported in a few children with neuroblastoma, one with atypical OMS in association with Turner's syndrome, consisting of seizures, and a Horner syndrome (88). Neuroblastomas, however, are positive for Hu antigen in ~75% of the cases even when seropositive for anti-Hu in only 4% (89).

In children, anti-neurofilament antibodies of molecular weight 210K were found in sera but not CSF from two children with OMS of presumed viral etiology, using an immunoblot technique (90). The disappearance of the antibody during adreno-corticotropic hormone (ACTH) treatments suggests clinical relevance; however, neurofilament antibodies found in the sera from normals, as well as several different degenerative neurologic disorders without OMS, may indicate a lack of specificity (91). In six other children with opsoclonus, circulating cerebellum-specific immunoreactivity was found with antibodies of molecular weight 27K, 35K, and 62K (92).

Cellular Immunity in Opsoclonus–Myoclonus

Whether OMS is primarily a B- or T-lymphocyte problem or involves both is unclear. There have been few studies of cellular immunity in OMS. The migration of leukocytes from children with paraneoplastic OMS was inhibited by neuroblastoma extract in a capillary migration test in vitro (34). Evidence for B-cell involvement is autoantibody production, although found in a minority of cases. Support for T-cell involvement is T-cell infiltrate in postmortem brain, and the fact that conventional immunotherapies for OMS more effectively target T cells than B cells; however, therapeutic failures therefore may argue against T-cell involvement. A slightly elevated helper-to-suppressor T cell ratio of 3.48 (normal range reported as 0.6–2.9) was found in a 14-month-old boy with OMS (93). In an adult patient with opsoclonus and breast cancer, suppressor T-lymphocyte function was depressed (94). Clinical relevance of this finding was suggested by the reversal of the abnormality with prednisone treatments in parallel with improvement of opsoclonus. However, the possible interaction of B and T cells and involvement of various effectors is unexplored. More fundamental research at this level is imperative.

Attempts to Develop an Animal Model

One of the difficulties with understanding the role of various paraneoplastic autoantibodies in OMS is that cause and effect have not been established. It is still not clear if these antibodies are directly involved in the pathophysiology. In an attempt to show that passive transfer of antibodies causes a paraneoplastic syn-

drome, guinea pigs were injected intracerebroventricularly with anti-Yo poly-
clonal IgG, which was obtained by plasmapheresis of a patient with a paraneo-
plastic syndrome and anti-Yo antibody (95). Although anti-Yo antibodies were
found in the cytoplasm of Purkinje cells immediately after and for up to 24 h after
the injection of anti-Yo antibodies; even daily injections failed to induce any
cerebellar pathology or any clinical abnormalities in the guinea pig, such as the
ataxia expected with anti-Yo. The immunostaining was found in brain cells other
than Purkinje cells as well. The authors raised several possibilities to explain the
negative results, the most probable of which may be that more than antibody
presence is required for the generation of a paraneoplastic syndrome (for instance,
cellular responses of the immune system). Although it is not clear that the guinea
pig would be capable of generating opsoclonus, it is a well-known animal model of
myoclonus. However, anti-Hu and anti-Ri autoantibodies rather than anti-Yo
would be required to test for opsoclonus or myoclonus. Anti-Hu monoclonal
antibodies developed in N2B/BLNJ mice, a strain reported to develop autoanti-
bodies more readily than other strains, induced no neurologic abnormalities
(84,96).

In Vitro Models

Recently, cellular responses to anti-Hu autoantibodies have been studied. As an
in vitro model, primary cultures of human brain cells containing both neurons and
glia were exposed to anti-Hu monoclonal antibodies (MoAb 16A11), which are
subclass $IgG_{2b\kappa}$ (97). After 48 h of exposure to anti-Hu 10 $\mu g/ml$, there was loss of
cell processes and death of neurons identified by immunostaining with a mono-
clonal antibody to a neuron-specific isotype of β-tubulin, c $\beta 4$ TuJ1, whereas glia
identified with glial fibrillary acidic protein were relatively spared. These data
suggest that primary cultures of human fetal brain are a model system for in vitro
molecular studies of autoantibodies in OMS.

It has also been shown that incubation of human neuroblastoma cells (BE2-N)
with monoclonal anti-Hu MoAb 16A11 in vitro results in apoptosis (98). Apopto-
sis, the morphologic correlate of programmed cell death (PCD) or "cell suicide,"
is characterized by cell shrinkage, membrane blebbing (zeiosis), a ladder appear-
ance to extracted genomic DNA, and breakup of the cell into membrane-bound
fragments (99). Unlike necrotic cell death, there is usually no spillage of cell
contents, so the glial and immune responses may be different (100).

However, other studies suggest that anti-Hu positive serum (polyclonal) is not
cytotoxic to different cell types in vitro, such as small-cell lung cancer cells
(NCI-H69) or pheochromocytoma (PC12) cells. Nuclear localization of anti-Hu
was not cytotoxic and did not interfere with cell proliferation in those cell lines
(101).

MECHANISMS OF AUTOIMMUNITY

As a point of comparison with autoimmune diseases and for construction of
hypotheses in OMS, it is useful briefly to review normal immune function (102).
The main components are lymphocytes, immunoglobulins, cytokines, and anti-

gen-presenting cells (Fig. 1). Lymphocytes determine the specificity of immunity and coordinate the effectors of the immune system, the cells that present antigen and mediate immunologic functions. The main classes of lymphocytes are T (thymus-dependent) cells and B cells.
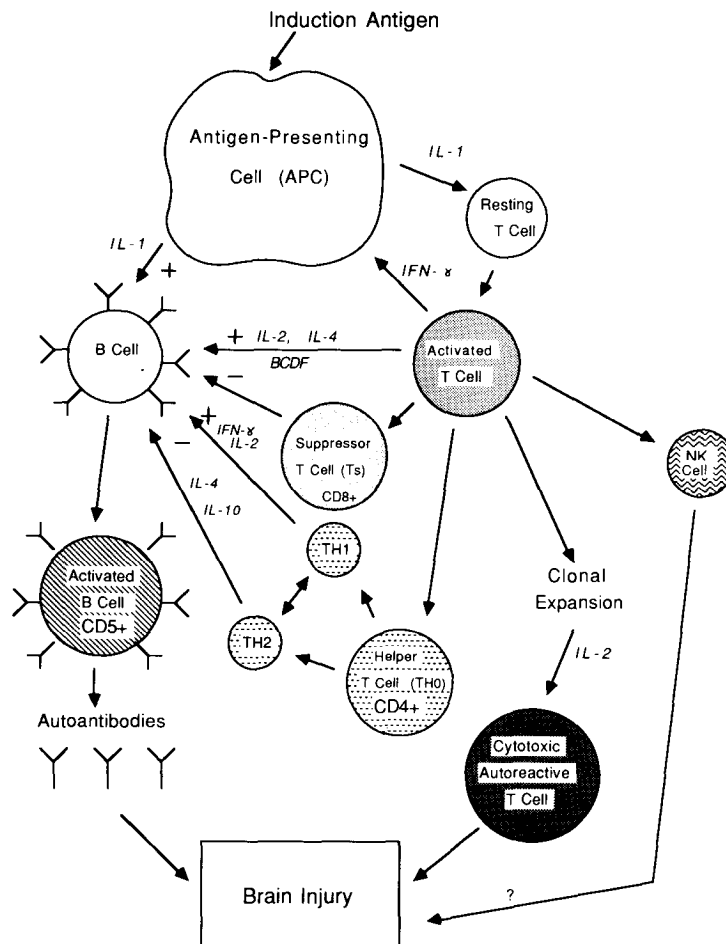
FIG. 1. Schematic overview of possible immune cellular reaction in OMS leading to brain injury. The antigen-presenting cell leads to activated T cells or directly stimulated B cells. The T-cell route involves the formation of various activated T cells with different functions, such as stimulating (+) or inhibiting (−) other cells. Suppressor T cells inhibit B cells but may also be cytotoxic, depending on the microenvironment. T cells may become cytotoxic autoreactive T cells via clonal expansion but also B-cell stimulation through the opposing influences of CD4$^+$ and CD8$^+$ T cells. There are opposing interactive CD4$^+$ cells. T_H1 cells stimulate B cells to produce IgG_{2a}, whereas T_H2 stimulate IgG_1 production. Activated B cells produce autoantibodies. Natural killer (NK) cells also could be activated to induce brain injury.

Normal Immune Function

Helper/Inducer T Cells

T lymphocytes that are identified by the surface membrane marker (cluster designation) CD4 are helper T cells (T_H). These cells recognize specific peptides presented by an antigen-presenting cell (APC) in conjunction with class II major histocompatibility complex (MHC; Fig. 2). This act of "recognition" plus other signals stimulates $CD4^+$ cells to divide and produce interleukins (ILs). $CD4^+$ cells facilitate antibody production by B cells and provide help for other T cells. $CD4^+$ cells may function as cytotoxic T cells instead of as helper/inducers (103). $CD4^+$ T cells can be subdivided into "naive" (unprimed) and "memory" (primed) cells, on the basis of their CD45 isoform expression: naive cells are CD45 RA^+, and memory cells are CD45 RO^+. Activated $CD4^+$ T cells can be subclassified on the basis of their cytokine-production profile into T_H0 [interleukin-2 (IL-2), IL-4, interferon-γ (IFN-γ), lymphotoxin], T_H1 (IL-2 and INF-γ), and T_H2 cells (induce B-cell growth and differentiation) (104). T_H1 and T_H2 cells cross regulate one another by release of their specific cytokines (IFN-γ and IL-4). Activation of T_H1 phenotype is often accomplished by silencing of the T_H2 phenotype and vice

FIG. 2. A closer schematic view of the molecular interaction between T cells and antigen-presenting cells (APCs) or target cells. T cells respond to an antigen through cell surface receptors (TCRs), whether foreign or self-antigen, in the context of the cellular environment. T cells will become activated only when the necessary cell adhesion molecules (B7, ICAM-1, various CD molecules) and costimulatory interactions are present, such as in the presence of inflammatory cytokines. This is called "professional" antigen presentation. Tolerance instead of activation results if APCs are "nonprofessional" or if inflammatory cytokines are counteracted by other cytokines released by tissue cells or other immune cells. Immunologically active cells will cooperate effectively only when they share major histocompatibility complex (MHC) haplotypes at either class I or class II loci (class I/II restriction). A: Helper T cell docks with APC presenting processed peptide fragment of circulating induction antigen. B: Autoreactive cytotoxic cell targets brain cell bearing autoantigen peptide.
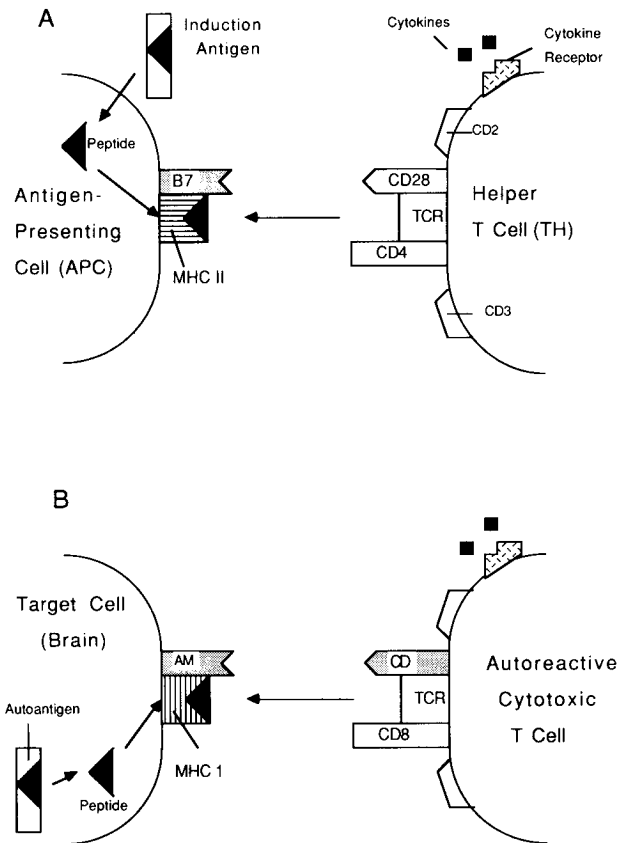
versa. Both may produce tumor necrosis factor (TNF)-α, granulocyte–macro-phage colony-stimulating factor (GM-CSF), and IL-3. T_H1 cells induce lympho-kine-mediated, complement-mediated, and antibody-dependent cell-mediated cy-totoxicity as well as delayed-type hypersensitivity.

Cytotoxic/Suppressor T Cells

Other T cells identified by the surface marker CD8 (cytotoxic or suppressor T cells), are programmed to recognize peptides associated with class I MHC [des-ignated by the human leukocyte antigen (HLA)-A, B, or C nomenclature]. Class I MHC presents internal antigens in the form of processed peptides (~eight amino acids; 105). Because MHC class I, which is present in all nucleated human cells, is the transplantation antigen, $CD8^+$ cells are cytotoxic to infected cells, grafts, or tumor cells. $CD8^+$ cells may also suppress or downregulate immune reactions. MHC class I gene products are expressed in response to viral, tumor, or trans-plantation antigens. All cells express the same class I MHC.
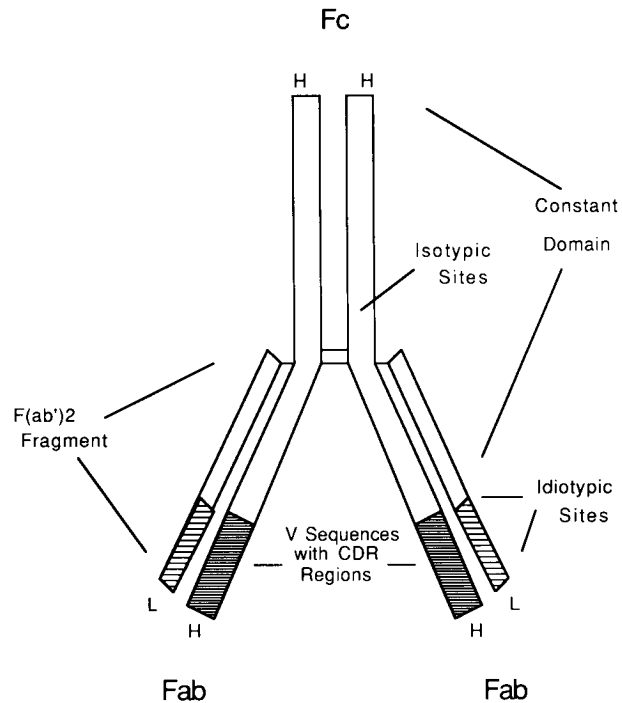
B Cells

B lymphocytes differ from T lymphocytes in several ways. B cells respond to antigens by production of immunoglobulins (Igs) not T cell receptors (TCRs) and expression of B cell–specific markers (106). The B cell's specific surface receptor is the immunoglobulin complex, and B cells secrete one type of antibody per cell, which binds to a select site (epitope) on a particular antigen. B cells may function as APCs in addition to their role in antibody production. Antigen undergoes endocytosis and processing in lysosomes. B-cell interaction with T cells leads to CD40 ligand production (107) and B7 expression. B cells secrete cytokines for Ig isotype switching. B cells activated to plasma cells secrete antibodies. B cells express specific antigens in their cell surface such as CD19, 20, and 21 (mature B cells). Most IgG antibody responses are "T cell–dependent," in that a $CD4^+$ cell must dock with the B cell, in addition to the binding of relevant antigen to the surface antibodies of the B cell. Some antigens (many carbohydrates), however, are "T cell–independent," but usually generate an IgM class antibody response. B- and T-cell responses to a single protein antigen are usually polyclonal (108). Activated B cells can also stimulate resting T cells to become activated.

Immunoglobulins

Immunoglobulins, the humoral immune system, are proteins synthesized by B lymphocytes and plasma cells that are important in immune regulation and host defense against infection (102). Antibodies are produced in response to antigens and recognize antigens without MHC restriction. The Fab section contains the antigen-binding site (Fig. 3). The Fc fragment, which binds to cells with Fc re-ceptors and to complement ($C1_q$ component), determines the antibody isotype or class (G, M, A, D, E) and subclass (G_1, G_2, G_3, G_4, S_1, S_2). Human IgG comprises four subclasses (IgG_1 through IgG_4) with different half-lifes, biochemistry, and structure. Antibodies to different antigens arise from different IgG subclasses:

Fc

FIG. 3. Diagram of human immunoglobulin (IgG). The structural components are described in the text. A radial arrangement of repeating IgG units makes up the pentameric structure of IgM.

H   H

Constant
Isotypic   Domain
Sites

F(ab')2
Fragment

Idiotypic
Sites

V Sequences
with CDR
Regions

L   L
H   H

Fab   Fab

Legend
V   Variable sequences
CDR   Complementarity determining regions
L   Light chain
H   Heavy chain

IgG$_1$ for tetanus and diphtheria toxoids, and IgG$_2$ for carbohydrate antigens (109). The Fc portion of the antibody protrudes from the cell, rendering the "target" cell susceptible to phagocytosis by various killer cells. Antigens have epitopes and determinants. A dominant epitope cluster on an antigen's surface is called a determinant. An antigen's epitope binds to an antibody's paratope. Variable (V) domains of the antibody are responsible for binding to antigen, whereas constant domains have effector functions. A single antigenic determinant on an antibody V region is an idiotype. The complementarity determining region (CDR) is the section of an antibody or T-cell receptor responsible for antigen/MHC binding. The two types of polypeptide chains contained by the antibody, heavy and light chains, are joined in a flexible hinge arrangement. Ig molecules are encoded by multiple genes.

Cytokines

Cytokines are peptide factors produced by T cells, macrophages, and related cells that function as local or systemic intercellular regulatory factors (110). Many

are principally T-cell products (lymphokines). The major groups include the interleukins (IL-1 through IL-12), interferons (IFN-α, -β, -γ), cytotoxic factors (tumor necrosis factor, TNF-α and TNF-β), differentiation factors (colony-stimulating factors), growth factors (transforming, platelet derived, epidermal, fibroblast), and intercrines (111). The "proinflammatory" cytokines include IL-1, IL-2, IL-4, TNF-α, and IFN-γ. In contrast, TGF-β is a general immunosuppressant. IL-2 and IL-4 are potent T-cell and B-cell growth factors, respectively, and IFN-γ controls the expression of class I and II MHC molecules.

Natural Killer (NK) Cells

NK cells are a population of lymphocytes that are distinct from the T- and B-cell lineage and make up ~5–10% of peripheral white blood cells. They possess intrinsic ability to recognize and destroy virally infected cells and tumor cells, playing a role in immune responses to infections and tumors. They display cytotoxic activity in an antigen nonspecific non–MHC-restricted manner (112).

Antigen-Presenting Cells (APCs)

Antigen-presenting cells in the periphery are chiefly macrophages and dendritic cells found in lymphoid organs (thymus, lymph nodes, spleen) but occasionally are B cells and other immune cells. In brain, microglial cells, phagocytic cells of the brain probably derived from the monocyte lineage, can present antigen. All "professional" APCs express MHC class II antigens (HLA-DP, HLA-DQ, HLA-DR; 113). To "process" antigen, APCs take up exogenous antigen by internalization or endocytosis, degrade it by lysosomal enzymes into short peptides (15 to 20 amino acid long fragments), and some of the peptides will combine with MHC class II molecules and be expressed on the cell surface (114). T cells do not recognize free antigens, but only peptides presented in the context of MHC. The antigen, MHC, and TCR for antigen constitute a trimolecular complex (115). MHC class II genes act as immunoregulating genes (116). Immune-response genes linked to the MHC locus define class II products on T and B cells and APCs. Other genes affect the rate of proliferation of differentiating B cells or macrophage antigen handling.

Normal Interactions Between Immune Cells

T cells and B cells normally interact to achieve a balanced immune response. Given the complexity of the immune system's task, to recognize and respond appropriately to internal or external antigens, it may be more surprising that errors in recognition of self, leading to autoimmune disease, do not happen more often. The immune system is regulated by cell–cell contact and secretion of factors (cytokines or lymphokines). The network theory, put forward by Jerne, proposes that T cells and B cells interregulate mutually by recognizing idiotypes on their antigen receptors. It is estimated that humans each possess 50–100 million different antibodies that must be regulated within a complex network. Natural autoreactive antibodies, which are directed against evolutionarily conceived mol-

ecules such as nuclear antigens or cytoskeletal proteins, are connected within a vast interactive network (117). That the presence of organ-specific autoantibodies may not tell the whole story is demonstrated by the finding of increasing autoantibody concentrations in healthy subjects with age, including anti-DNA, anti-brain, anti-myelin, anti-tubulin, and anti-neural tissue antibodies. The subtleties of how physiological autoreactivity in most individuals does not lead to pathological autoimmunity are not understood. There are several mechanisms for tolerance to self.

Breakdown of Immunological Tolerance

Autoimmune disease is the clinical expression of autoimmunity. The complexity of interactions between components of the immune system is beyond the scope of this review, but a simplified summary provides a useful basis for discussion of hypotheses of OMS.

Mechanisms of Autoimmunity

Autoreactivity is physiological and necessary to avoid pathology (118). A physiological equilibrium exists normally between the immune system and all self-molecules. Autoimmunity is both a qualitative and quantitative concept: the type, amount, affinity, or duration of antigen, autoantibody, or autoreactive T-cell activity. Even with an antigen regarded as "foreign," the amount or concentration of antigen is important in determining the immune response: higher concentrations are more likely to be immunogenic (119). The multiple redundant immunoregulatory mechanisms that prevent autoimmune responses to self-antigens include cell-mediated suppression, anergy, and regulatory "anti-idiotypic" antibodies (120).

B cells are capable of recognizing many self-antigens, so there are "naturally occurring autoantibodies." The antibody V-region is important, participating in idiotype–anti-idiotype regulation. Natural autoantibodies are multireactive. Pathological autoantibodies may occur as a result of abnormal expansion of natural or somatically mutated autoreactive clones (117,121,122). The mere presence of autoantibodies does not establish pathogenicity. Autoantibodies may be produced to an organ after damage to that organ by another means. Most commonly, autoantibodies are "footprints" of an etiologic agent, not a cause of damage (123). Autoantibodies directed against cell-surface targets are pathological, whereas those against extracellular or intracellular targets may not be (122). Cell-surface targets include adhesion molecules, neurotransmitter receptors, hormone receptors, or membrane gangliosides.

Despite a comprehensive developmental program to delete or render unreactive (clonal deletion or anergy, respectively) T cells that do not "learn tolerance" (124), some T and B cells potentially responsive to self persist (autoreactive) without clinical manifestations under normal circumstances (125). Autoreactive B cells and T cells may represent 10–20% of all lymphocytes in the spleen. However, all antigens cannot be expressed and presented in the maturing thymus during T-cell learning of self-tolerance (126). Therefore, some T cells possess

receptors capable of recognizing organ-specific self-antigens, specifically those "cryptic" or "subdominant" determinants that are not processed and presented efficiently and are therefore unable to tolerize developing T cells (125). An antigen may not induce an immune response unless in the presence of a costimulant (virus, tumor, vaccine adjuvant), and many costimulations are required for T-cell activation (127). Autoimmune responses may be triggered by exposure to cross-reacting antigens, exposure of normally hidden antigens, or impaired immunoregulatory mechanisms. The clonal-balance concept suggests that even a small shift in the helper/suppressor ratio may lead to autoimmunity (116). Although there are many types of activated B cells, CD5$^+$ B cells are found only in low numbers in normal individuals but have a propensity to recognize autoantigens and are more prominent in various autoimmune disorders (128). Once the boundary between autoimmunity and autoimmune disease has been crossed, autoaggressive infiltrating cells attack normal tissue.

Response to Viruses

Viral infections may have a role in the spontaneous occurrence of autoimmunity (129). Virus particles are recognized as foreign and are eliminated by the immune system. Some viral peptides resemble a "self-antigen." Immune cells primed to these viral peptides will attack cells expressing the "cross-reactive" self-antigen even after the viral infection is under control, resulting in autoimmunity. Activated T cells can collaborate with B cells to produce autoantibodies. Viruses may induce autoantibodies by releasing autoantigens from virally infected tissue when cells are lysed, encoding antigens bearing molecular similarities to self-proteins, or by nonspecific polyclonal stimulation of B cells (130). These autoantibodies usually disappear gradually over months. During IgM to IgG isotype switching, IgG antibodies do not crossreact with the normal tissues (131). Viral infections may also stimulate the release of IFN-γ and induce class II MHC expression, therefore increasing the likelihood of other cells becoming APCs. Bacteria, drugs, and environmental chemicals could have the same effect. However, not all viruses result in activation of the immune system, and under certain circumstances some, such as cytomegalovirus and herpes virus, may be immunosuppressive.

Responses to Tumors

Tumor cells may stimulate many different cellular immune responses involving macrophages, cytotoxic or helper T lymphocytes, and NK cells (132). The helper T cells release cytokines, recruit other immune effectors, and modulate B-cell antibody production. The T-cell repertoire against cryptic self determinants may be a crucial defense against tumors (125). Antibody-dependent cell-mediated cytotoxicity refers to the rendering of granulocytes, monocytes, and NK cells tumor selective in the presence of specific antibodies. Cytokine-activated lymphocytes (lymphokine-activated killer cells; LAKs) can also participate in controlling tumor growth as demonstrated by detection of the cells in tumors of cancer patients. Tumor-infiltrating lymphocytes (TILs) are found in tumors from cancer patients (7,9). TILs need not be LAKs.

Class I MHC plays a role in tumor growth and metastasis (133,134). Class I MHC is expressed by neuroblastomas (89), but cultured neuroblastoma cells express little or no class I MHC (135). Aberrant expression of MHC II molecules on cells (ectopic or heterotopic) may initiate an autoimmune response (136). IFN-γ can induce class II MHC expression (137). Decreased class I MHC expression was found in human small-cell lung cancer (138).

Tumor antigens (denoted here with arabic rather than Roman numerals to avoid confusion with MHC classification) include those found only in the patient's own tumor cells (class 1), those shared by tumors of similar types (class 2), and others found in both normal and neoplastic cells (class 3) (139). Many tumor antigens bear T cell–independent (carbohydrate or glycolipid) or tolerated determinants. Tumor antigens recognized by the cellular and humoral immune system may differ.

Because neuroblastomas secrete catecholamines, it is noteworthy that catecholamines can modulate immune function such as lymphocyte proliferation, cellular migration, and antibody secretion, and that both cytokines and neural signaling molecules act through the same second-messenger systems (140). The presence of mostly β_2-adrenoceptors on lymphocytes suggests that epinephrine may be more influential than norepinephrine. Besides circulating catecholamines, some lymphoid parenchyma has dense sympathetic innervation (141). Treatment with glucocorticoids may upregulate lymphocyte β-adrenoceptors (142).

Brain–Immune System Interactions

Relevant to autoimmunity and the brain is the interaction and potential for cross-reactivity between the brain and the immune system. A monoclonal antibody against human T lymphocytes (UCHT1) labels Purkinje neurons (143). One of the NK markers, CD56 (144), is also a neural cell adhesion molecule (NCAM-1) (145). Several cytokines affect immune responses of the CNS (146). TNF-α and IFN-γ stimulate astrocytes and microglia to proliferate (147,148), to function as APCs (149), and to secrete cytokines (150). Interferon-α can affect the cell firing rate at several brain loci (151). Cells of the CNS respond to cytokines and can be stimulated to produce cytokines, such as IL-1, IL-6, GM-CSF, and TNF-α, produced by cultured astrocytes (152–156). Cytokines may be some of the environmental signals required in the CNS to direct brain cell lineages during development (157).

Special features of immune surveillance in the CNS have been reviewed recently (158). The brain, an immunologically "privileged" site due to the blood–brain barrier and lack of native lymphoid cells, is both protected and potentially vulnerable to immune system attack for different reasons. Nonactivated T cells are probably incapable of crossing the blood–brain barrier and are present normally in undetectably low concentrations (159). Even activated T cells that enter brain, in the absence of restimulation by a foreign antigen in brain, return to the circulation. Brain does possess microglia and resident macrophages, which can act as facultative APCs, but they act at the blood–brain interface, minimizing parenchymal lymphocytic infiltration (160). Low expression levels of genes for

both MHC classes help protect against induction of autoimmunity in the CNS. MHC antigen expression is inducible on microglia but not readily on neurons or oligodendroglia. Conversely, antigens in brain are potential targets for autoimmune reactions because T cells usually were not exposed during development of the immune system to the antigens in this protected site. Brain antigens that "leak" into the blood after brain injury may be regarded as foreign and provoke continued autosensitization.

Examining the Components of Autoimmunity in OMS

The major components of autoimmunity are genetic, hormonal, and environmental. On the basis of abnormalities in other autoimmune diseases, these issues should be considered in OMS. Although a genetic vulnerability for OMS is certainly plausible, no direct data support such a hypothesis. Given the multiplicity of genes involved in the regulation of various components of the immune system, the possibility of genetic factors has not been tested. A subset of children does exhibit a genetic predisposition to develop neuroblastoma (23,161,162), but OMS does not occur in siblings and has been reported only in second cousins (163). There is no evidence of OMS in monozygotic twins, first-degree relatives of the patient, or an increased incidence in families. Many diseases associated with HLA antigens are autoimmune, but HLA studies have not been performed, nor has an increased incidence of common autoantibodies in patients and first-degree relatives been sought. However, the likelihood of HLA association for OMS is low in the absence of a familial predisposition or other autoimmune disorders. There are no data about GM-allotypes or complement-component deficiencies. Genetic factors influencing the immune response have not been evaluated in OMS, including genes linked to the MHC locus or Ig system.

Both IgA deficiency and complement deficiency are found in some other autoimmune disorders. Regarding defects in the immune system, no IgA deficiency has been documented in OMS. There have been no reported determinations of complement-component deficiencies, qualitative and quantitative defects in T suppressors, defects in NK cells, defects in secretion of, response to, and receptors for IL-2 and other lymphokines, or defects in phagocytosis.

There is no evidence to support hormonal factors in autoimmunity in OMS because prevalence of disease is not increased among females or in Klinefelter's syndrome. Autoantibodies are not known to be more prevalent among females. OMS is not a disorder that is exacerbated during puberty, pregnancy, or in the postpartum period, and there are no data on the effects of contraceptives on patients who have had childhood-onset OMS. Hormones and corticosteroid problems are also unexplored.

Environmental factors are likely to be very important in OMS, including infecting agents such as viruses or bacteria and immunizations or vaccinations. Assessment of the potential effects of immunization on the onset of OMS is not simple. Even at the mean age of onset of 18 months in pediatric OMS, most of the children will have had immunizations with diphtheria-pertussis-tetanus (DPT) or measles-mumps-rubella (MMR). Many parents relate the onset of OMS shortly after one

such immunization. The immune system may remain activated for weeks to months, obscuring any superficially obvious temporal association with the onset of OMS. Although the task force on DPT immunization of the Child Neurology Society came to largely negative conclusions when the broad spectrum of pediatric neurologic disorders was reviewed (164), the situation with OMS, as a putative autoimmune disorder, may be a special case in need of epidemiologic study.

HYPOTHESES OF OMS

Hypotheses toward an operational theory of OMS must take into consideration the key clinical features and differences in the syndrome in children and adults. Several hypotheses with corollaries are proposed (Table 4). In some instances, available data are insufficient to choose between alternative hypotheses.

The OMS syndrome appears to be a monophasic disorder of immunoregulation, a single-organ autoimmune disease, with neural tissue as the principal target (brain most often with or without peripheral nerve or autonomic ganglia in different or variant paraneoplastic disorders). The immune mechanism may be a type II or type IV hypersensitivity reaction, incorporating evidence that autoantibodies alone seem insufficient to induce the syndrome without, presumably, a cellular immune (T-cell) response. Type II hypersensitivity requires antibodies and is associated with many autoimmune diseases. Type IV hypersensitivity is mediated by T cells as in graft-versus-host reactions. The initiating or instigating event is peripheral to the CNS. This hypothesis rejects the notion of direct viral invasion of the brain or brain injury by tumor substances toxic to brain, both of which would initiate events in the CNS instead, but for which there are no supporting

TABLE 4. *Hypotheses on the immunopathophysiology of OMS*

1. OMS is a type II or type IV hypersensitivity reaction, single organ (neural), a disorder of immunoregulation
   a. Usually self-limited, but time frame unknown
   b. Monophasic, sometimes relapsing
   c. Immune dysfunction begins outside the CNS
   d. Tumor or virus are induction antigens or altered self-antigens (molecular mimicry)
   e. The immune response is initially appropriate but is secondarily pathologic
   f. MHC class I or II presentation of antigen may be involved or "superantigen" binds directly
   g. Neural tissues are antigen-bearing cells or neoantigens and targets of immune response
   h. In children, immunization may sensitize immune system to next presenting antigen (two-hit corollary)
2. Aberrant immune function in OMS injures brain and induces neurologic dysfunction
   a. Circulating autoantibodies may directly injure brain cells after gaining entry to the CNS
   b. Autoantibodies may be produced by B cells *in situ* in the CNS
   c. Cytokines may open the blood–brain barrier for autoantibodies, may be directly injurious themselves, or may amplify CD4$^+$ and CD8$^+$ responses
   d. Activated T cells can enter the CNS and could cause injury by several different mechanisms
   e. Secondary antigen-specific cellular and humoral immune responses may develop
   f. There is no widespread inflammatory component
   g. Either neurons or glia could be the target cells, depending on the autoantibody or T cell
   h. Dedifferentiation is a possible alternative mechanism of brain dysfunction to cell death
   i. Developing brain may have special vulnerabilities

OMS, opsoclonus–myoclonus syndrome; CNS, central nervous system; MHC, major histocompatability complex.

data. Diverse pathogens or neoplasms could break immunologic tolerance to a self-antigen, and the clinical outcome would depend on the magnitude of autoaggression and tissue specificity of target antigens. The other alternative to a peripherally originating immune system pathophysiologic event is a primary CNS process that allows CNS antigens to escape into the periphery, for which there is also no support. Whereas a subclinical viral infection could have this effect, no similar mechanism could be proposed for paraneoplastic cases.

Two opposite problems with the immune system seem to occur in OMS, especially the paraneoplastic form. The first problem may be a defect in immune surveillance, whether a "stress response" (165) or genetic vulnerability, which decreases immune responsiveness and increases susceptibility to infection or tumor growth. The second problem appears to be an immunological overreaction or hyperresponsiveness on some level that, in conferring better tumor survival than in nonparaneoplastic cases of neuroblastoma or recovery from infection, also damages brain. Given the diversity of etiologic agents in OMS, the most economical interpretation of the data is that the mechanism of anti-tumor or anti-viral immunity, however different at the outset, may share the same final common pathway, one that leads to an autoimmune brain disorder.

Peripheral Induction

Predispositions

Several factors may contribute to the sequence of events leading to immune system dysregulation in OMS. In children, the immune system may become overactive because of the high frequency of viral infections, which average 10 or more yearly during infancy. Immunizations, which precede the onset of OMS in some pediatric cases, may be another predisposing factor. Immunizations, designed to "boost" the immune system against specific antigens, which are given repetitively and overlap with the mean age of onset of OMS (166), initially activate T cells (generalized activation). The stimulation may last several weeks. This is also a time of increased activity and proliferation in the development of the immune system, reticuloendothelial system, and thymus gland, and the young immune system is more easily primed (103,167). These factors may be relevant to pediatric but not adult-onset OMS.

The capacity of tumor or viruses to induce MHC expression also may be an important variable and vulnerability. Tumors that induce MHC expression may be more immunogenetic. Conversely, tumors with little MHC expression may have increased growth and metastatic potential.

Disease-Specific Autoantigens

The disease-specific autoantigen is unknown or "cryptic" (Fig. 4). The induction antigen, be it neoplastic or viral, is presented to the peripheral immune system, where the macrophage is often the antigen-processing immune cell and

FIG. 4. Possible mechanisms of antigen formation in opsoclonus–myoclonus (OMS). The induction antigen in neoplastic cases may be an onconeural antigen, produced by the tumor, or naturally occurring in brain or similar in structure to a natural self-antigen. The immune system, not previously exposed to this "brain antigen," has no mechanism of inducing tolerance to self now in the setting of tumor-expressed major histocompatibility complex (MHC). In postviral cases, virus bears a molecule resembling a brain ligand (molecular mimicry). The presence of a cross-reactive epitope on the virus may also present a tolerated antigen on a nontolerated carrier. Alternatively, virus could give rise to anti-idiotype molecules, which could act as "surrogate" autoantigen.
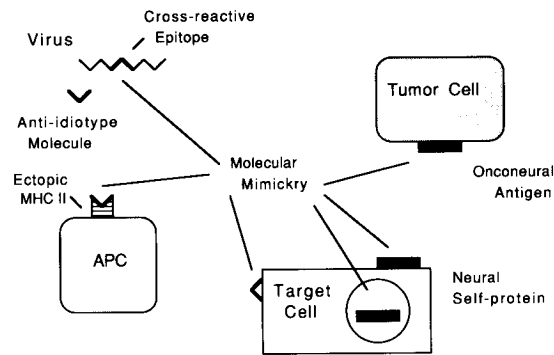
may bind to expressed class 1 or class 2 MHC (115). Alternatively, the induction antigen may be a "superantigen" that directly stimulates T cells without intracellular processing (168). A superantigen is an antigen that is especially effective in causing selection of T-cell populations expressing the same variable $(V\beta)$ domain and skewing of the TCR $V\beta$ repertoire. It activates up to 20–30% of peripheral T cells, rather than the <1% stimulated by conventional antigens (169), and binds to the $V\beta$ portion of the TCR β chain (170). Superantigens could activate autoreactive T cells. In paraneoplastic cases, the induction antigen may be a Class 2 tumor antigen. There may be more than one autoantigen.

Molecular Mechanisms

While the initial immune response is appropriately directed to eradicating virus or tumor, the immune response becomes secondarily pathological. Because the immune process in OMS is initiated outside the CNS, how are autoreactive T cells activated to attack brain in the absence of brain autoantigen? Possible mechanisms include molecular mimicry or activation by superantigens. T cells activated by a viral infection or neoplasia could activate autoreactive T cells as bystanders once T cells are stimulated through the CD3/TCR or CD2 activation pathways. Activated B cells may also stimulate T cells.

In molecular mimicry, structural homology between a self-protein and a pathogen or tumor antigen triggers a cross-reactive B- or T-cell response (171). Molecular mimicry either by antibodies or by T-cell epitopes after infections has been implicated in organ-specific autoimmunity. Cryptic determinants may become displayed during the course of inflammatory events during an infection, activating the corresponding potential T-cell repertoire and widening autoimmunity through molecular mimicry (125). Even an identical six-amino-acid sequence between two otherwise dissimilar proteins, a situation with estimated 1 in 20 million odds of occurrence, could be sufficient to provoke recognition of self as foreign antigen.

The foreign and host determinants must be similar enough to induce cross-reactivity but different enough to break immunologic self-tolerance (172). A slight discrepancy rather than exact homology is even more likely to trigger an immune response. Molecular mimicry may be prompted by the tendency of viruses to try to evade the immune system by changes in antigenicity of their surface antigens. There are many examples of molecular mimicry between virus and self, including measles virus P3 and corticotropin or myelin basic protein, hepatitis B virus polymerase and myelin basic protein, herpes simplex virus and the human AChR, papilloma virus P2 or rabies virus glycoprotein and the insulin receptor, human immunodeficiency virus and astrocytes, and Epstein–Barr virus and nine different self-antigens (131,171,173). Molecular mimicry can also occur with bacteria, such as with *Campylobacter jejuni* and anti-GQ16.

Cross-reactivity between neural crest–derived tumors and brain antigens (on-coneural antigens) in paraneoplastic cases is also very plausible, given their shared embryology (174). Tumor-associated antigens, which may be the result of carcinogenesis, include intracellular and cell-membrane antigens such as self-proteins (fetal antigens), oncogene products, mutated tumor-suppressor gene products, and nonmutated cellular proteins (8,134). Normal proteins may be antigenic if expressed aberrantly or in supranormal concentrations (175). For T-cell recognition, the primary amino acid sequence rather than the three-dimensional conformation is necessary (176).

Multiple Induction Mechanisms

More than one induction site is probably involved in OMS because some mechanisms do not require T-cell activation. Epstein–Barr virus, one documented viral cause of OMS, is well known directly to induce polyclonal activation of B cells to produce autoantibodies. A pathophysiologic model with multiple immunologic induction mechanisms or sites of entry into the cycle of immunopathology with a final common pathway of dysfunction would be compatible with the scant data available.

The Autoantibody Problem

Why are serum autoantibodies seldom found in OMS, especially in children, if autoantibodies have a direct role in the pathophysiology of OMS? There may be a sampling problem—a short period of elevated blood levels very early in the disorder corresponding to the induction of brain injury. There may be a concentration problem, with low circulating autoantibody levels in most patients, reflecting the capacity of tumor to present antigen to the immune system. Are the clinically relevant antibodies being measured especially in pediatric OMS? Given the large number of circulating antibodies and the presence of normal circulating autoantibodies, the task of identifying the relevant autoantibodies in OMS is a difficult one. There may be many other types of autoantibodies currently undetected. It is also possible that autoantibodies are an epiphenomenon.

Brain Injury

Blood–Brain Barrier

The next step in the immune attack against brain is crossing the blood–brain barrier (Fig. 5). The four main candidates for inducing injury are circulating autoantibodies, activated B cells, activated T cells, and cytokines. Activated T cells can penetrate or breach the normal blood–brain barrier (160,177) or migrate through altered tight junctions (178). The activation state of lymphocytes rather than T-cell phenotypes, MHC compatibility, or antigen specificity is the main factor (177). Activated B cells may also "traffic" into the CNS, but it is unknown whether they follow a lead cell, such as an activated T cell. B-cell trafficking would explain the intrathecal synthesis of Ig reported in paraneoplastic syndromes and other neurologic disorders. Cytokine production also may allow circulating autoantibodies to penetrate into brain. The blood–brain barrier is not very permeable to autoantibodies; the barrier permeability is not absolute but relative to variables such as molecular size: normal CSF levels of IgG are 0.2 to 0.4% of plasma levels (179).

FIG. 5. Simplified view of how lymphocytes activated in the periphery may induce brain injury in opsoclonus-myoclonus (OMS). Activated T cells have access to brain and, transformed to cytotoxic autoreactive T cells, would be able to injure brain cells directly or through cytokine production. Activated B cells, which also enter brain, could locally produce antibodies that injure brain cells, such as cytotoxic or blocking antibodies. T cells may be involved in the activation of B cells. Alternatively, autoantibodies produced outside brain could gain entry across the blood–brain barrier through the help of cytokines produced by T cells in higher concentrations than possible without barrier disruption. The antigen-presenting cell (APC) in brain in OMS may be neuronal (N) or glial (G). In the absence of factors such as major histocompatibility complex (MHC), to make these cells professional APCs, no immune autoaggression takes place. Activated T cells that do not encounter APCs exit brain.
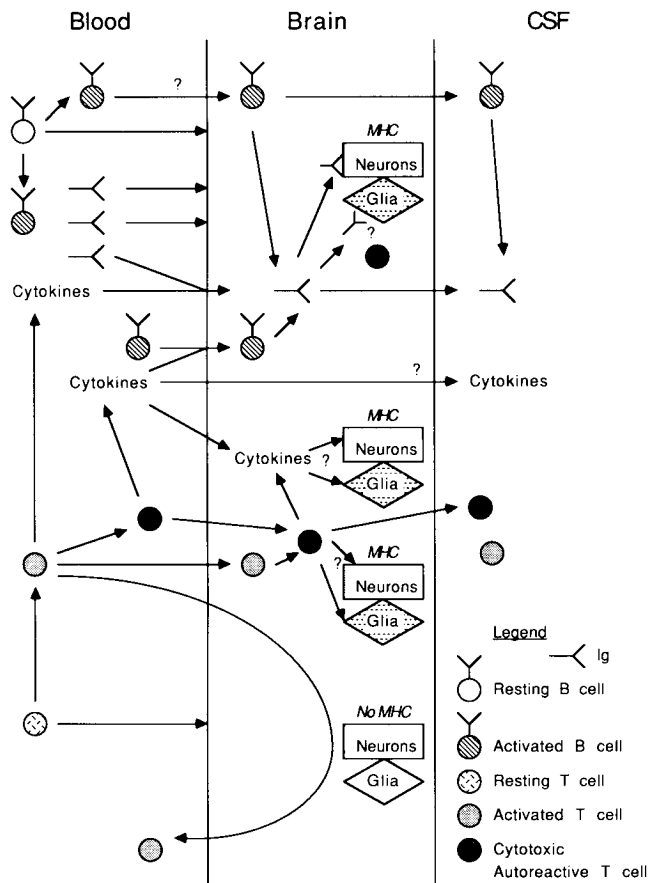
Target Cells

The target neural cell in brain may be neuronal or glial, or a subcellular component such as that involved in synaptic cytoarchitecture or neurotransmission. Neuronal–glial interactions important in brain development (180) may be affected. Autoantibodies found so far in OMS have been anti-neuronal. There is no evidence of widespread brain cell death, inflammation, blood–brain barrier disruption, or demyelination (Table 5), but focal abnormalities or involvement of select cell subpopulations is likely. If the target cell is neuronal, why are all neurons not attacked? One hypothesis is that cells are attacked on the basis of neurotransmitter expression or enzymes involved in neurotransmitter metabolism, such as the antibodies against glutamic acid decarboxylase (GAD) found in stiffman syndrome and palatal myoclonus (55,181). A T_H1 T-cell response to GAD has been demonstrated experimentally (182). With the recent evidence for dysfunction of monoaminergic neurotransmission in pediatric OMS (183), targets within serotonergic or catecholaminergic systems also are plausible.

What other properties confer vulnerability to attack? Presumably, the target cell must also express MHC antigens. Neurons have little MHC class I (184) and the expression of MHC class I and class II genes in normal brain is low (160). There are no data to discern whether microglia, which can express MHC class II antigens (185), are involved in OMS, but astrocytes can function as APCs (149,186). Structural damage to the target organ may create a "vicious circle" of further autoaggression by releasing further antigen.

Type of Injury

Much of the discussion has centered on cell death as the type of brain injury and apoptosis as a possible mechanism. This is most relevant to the adult-onset syndrome in which brain atrophy and necrosis occur. Even in pediatric-onset OMS, the death of small but functionally significant populations of specific neurotransmitter-containing cell types, such as serotonin-containing cell bodies (representing only a small percentage of brain neurons), would not be detected by conventional neuroimaging techniques. Small lesions of critical neuronal networks could have profound effects. However, if cell death occurs, it is not widespread, especially in pediatric OMS. What are alternative sublethal types of brain injury?

TABLE 5. *Arguments against a widespread brain abnormality in pediatric OMS*

Not widespread	Reason for conclusion
Blood–brain barrier disruption	No cerebral edema on CT or MRI scans
Attack on myelin	No demyelination on MRI scans
Cell death	Majority of pediatric cases have normal head size and growth; usually no brain atrophy on neuroimaging studies
Inflammation	No enhancement on CT or MRI scans

OMS, opsoclonus–myoclonus syndrome; CT, computed tomography; MRI, magnetic resonance imaging.

Immunologically mediated dedifferentiation could cause neurologic dysfunction without cell death. Synaptic injury could also be functionally serious but sublethal and currently undetectable. Whatever type of brain injury occurs appears to happen early, perhaps over hours to weeks, and may be irreversible without early therapeutic intervention.

Mechanism of Injury

Brain injury in OMS may be caused by several different mechanisms: direct attack by antigen-specific T cells, nonspecific lymphocytes such as NK cells or $\gamma\delta$ cells, cytokines released by activated cells, or autoantibodies (IgG or IgM) (187,188). Some subsets of cytotoxic T cells ($\gamma\delta$) possess NK cell–like cytotoxic activity (189). Cytokines may be secreted either by immune cells (T cells and macrophages) or CNS cells (glia). The immune system may damage or destroy target cells through antibodies, complement, and cytotoxic cells by perforating cells (allowing osmotic lysis), cross-linking membrane proteins, blockade of receptor sites, activation of programmed cell death, and other mechanisms (102).

Clinical Correlation

Heterogeneity

There is clinical, immunologic, and pharmacologic heterogeneity within pediatric OMS (190), differences that are well known among paraneoplastic disorders in adults (10). In children, phenotypic differences in OMS are seen (190), with a significant clinical subgroup manifesting predominantly ataxia, but another group may have chiefly behavioral and cognitive problems. Even in the presence of other clinical signs, one symptom or sign may predominate. Because autoantibodies are seldom found, biological subgrouping has not been possible. The overlapping syndrome of acute cerebellar ataxia of childhood is a phenotype not currently identified as a paraneoplastic syndrome. Opsoclonus–myoclonus–ataxia is the most common syndrome, but the proportion of component features is variable (1). The etiologic heterogeneity of OMS involves presumed postviral and paraneoplastic etiologies. Immunologic heterogeneity includes presence or absence and type of autoantibodies or immune-cell defects. Pharmacologic heterogeneity in OMS includes responses to ACTH or corticosteroids and other immunomodulatory drugs. Heterogeneity in OMS could be explained by multiple immunologic mechanisms, giving rise to different clinical features, differences between patients in extent of immune-mediated brain injury or sites of injury, or differences in recovery mechanisms or success of reorganizational events in restoring brain function. The regional targets of brain injury may be predominantly subcortical but probably involve multiple structures (1). Even the heterogeneity in prodrome features of OMS may provide clues to the immunologic injury: Are the profound irritability or unconsolability, sleeplessness, or vomiting site or mediator specific? Are they effects of one or multiple pathophysiologic agents?

Remissions, Relapses, and Progression

Remission and recovery in OMS are not surprising because self-limiting immunologic diseases are common. The disappearance of reactivity to self may occur after an immunoglobulin isotype switch, such as from an initial IgM response that changes to IgG during the maturation of an immune response (171). Failure to remit or recover, which is more common in patients with severe OMS, may indicate more than a transient exposure to induction antigen. Further immune dysregulation would be required once autoreactive T cells become activated for all but a brief immune attack on brain. Otherwise, T cells return to a resting state. Long-term maintenance of cytotoxic T-cell memory does not require persistence of antigen (191).

The perplexing practical question is how long does immune system dysregulation persist in OMS? Do clinical relapses induced by intercurrent illnesses or withdrawal from ACTH or corticosteroids represent further bouts of immune dysregulation or indicate merely the presence of unmasked brain injury? The peripheral immune system may be in a fluctuating state of activation from persistent stimulation by antigens (exogenous or endogenous) or lack of suppression of B and T cells. The further stress on the immune system of dealing with new infections may impair the immune system's capacity to dampen or downregulate aberrant responses. That some patients do not relapse suggests a mild course or a shortened period of immune dysregulation.

It is tempting to speculate that one possible explanation for the progression of adult cases and nonprogression of pediatric cases may be the flexibility or resilience of the pediatric immune system in being able to reregulate. Age-related differences in numbers or functions of immune components may be a variable. Other explanations include different immune mediators or different capacities for recovery.

Mechanism of Current Treatments

Current treatments for OMS may work through immunomodulation, because they have a multiplicity of effects on immune system function. Because of their many effects, the exact site of therapeutic efficacy in OMS is unknown. Failure of these various treatments in some patients could be the result of several factors. Brain injury may have occurred before the initiation of therapy. Treatments may have limited capacity to reverse the immunologic abnormality or, unlike the instigating immune process, may not have access to the CNS.

IMMUNOTHERAPY OF OPSOCLONUS–MYOCLONUS

Overview of Current Treatment

The treatment of OMS is variable and somewhat idiosyncratic. Paraneoplastic cases are treated differently from paraviral cases, and pediatric-onset cases differently from adult-onset cases. Given the frequency of poor long-term responses to treatment, the therapy of OMS should not be regarded as absolute, but should be challenged and rethought. A reasonable assumption is that brain injury occurs

early, maybe much earlier than now appreciated, and immunomodulation should begin immediately, but the priority of treatment options is uncertain. What sets OMS apart from other better characterized autoimmune neurological disorders such as myasthenia gravis and multiple sclerosis is that it is usually self-limited and nonprogressive. Treatments such as thymectomy are not considered. OMS in some respects is more similar to Sydenham's chorea and Guillain–Barré syndrome. Some treatments should be aimed at inducing a remission, whereas others are most useful in maintaining the remission. When possible, the choice of an immunosuppressive agent should be based on the underlying disease mechanism. An immunotherapy that helps one disease may not necessarily help another. Cell-mediated immunity is sensitive to cyclosporine and anti-lymphocyte antibodies and less sensitive to azathioprine and corticosteroids. Antibody production is sensitive to alkylating agents and less sensitive to high-dose steroids and thiopurines (192). Most treatments that target lymphocytes are more effective against T cells than against B cells. Current therapies have limited capacity to remove autoantibodies that have crossed the blood–brain barrier or bound to target neural tissues (193).

Treatment of the Tumor

If a tumor is found, it is typically removed. In paraneoplastic cases, there is a theoretical conflict between the urgency to start treatment for the neurologic syndrome to avoid permanent brain damage and the concern about suppressing the immune system's response to the tumor. This may be a moot point because the tumors tend to be more benign in children with OMS than their counterparts, but the contribution of host (immune) versus tumor factors has not been explored. When a tumor is found, immunotherapy is usually delayed. The tumors found in pediatric OMS are small and seldom invasive or metastatic. Treatment of the underlying tumor in paraneoplastic cases is more likely to improve OMS in children than in adults, in whom the neurological symptoms may progress anyway. Treatment of the tumor should on theoretical grounds decrease the antigenic challenge. Yet some patients worsen when the tumor is resected, possibly because more antigen is released into the circulation. In patients exhibiting paraneoplastic autoantibodies, antibody titers may persist for years after tumor resection. Antibody persistence probably results from immune dysregulation, allowing survival of autoreactive lymphocytes, but a continuing antigenic challenge is also possible.

ACTH and Corticosteroids

The use of ACTH and glucocorticoids is a major therapeutic modality in pediatric OMS (for review, 1), but is not effective in adult-onset OMS (73,194) except in a subgroup (81). In the absence of controlled trials, the superiority of ACTH to steroids in pediatric OMS, which has been the experience of the National Pediatric Myoclonus Center, is unproven. ACTH and steroids may be symptomatic therapy. Initial responsiveness to ACTH in children has been reported to be as high as 80–90% of cases, but patients frequently relapse during the time of ACTH

or steroid withdrawal. Therefore, some patients have not been withdrawn completely from ACTH or steroids for years. This increases the well-known side effects of ACTH and steroid therapy. Because steroids suppress the immune system for a longer duration than pituitary ACTH secretion, alternate-day steroids are used in the tapering and maintenance phase of treatment. Response to ACTH and steroids is not universal and does not differentiate patients with and without tumors. $ACTH_{1-39}$, $ACTH_{1-20}$, and the synthetic $ACTH_{1-24}$ have been used successfully. Steroids have included prednisone, dexamethasone, prednisolone, triamcinolone, betamethasone, hydrocortisone, and other steroids. The doses and regimens of ACTH for OMS are similar to those which have been used for infantile spasms. Failure of response or tolerance to ACTH should suggest an underlying tumor or the presence of anti-ACTH antibodies. Autoantibodies to ACTH were found in an 8-year-old boy who had been treated with ACTH for years but not in several other children treated for a shorter time (195).

Mechanism of Action

The mechanism of action of ACTH and corticosteroids in OMS is unknown. Both ACTH and steroids may have direct effects on brain (for review, see 196). ACTH may also close a pathologically opened blood–brain barrier (197). It has been argued that corticosteroids exert their major effect by antiinflammatory rather than immunosuppressive mechanisms, such as inhibition of phospholipase A2 synthesis and stabilizing effects on lysosomal membranes and neutrophils. Both ACTH and corticosteroids also have many immunosuppressant effects, which may be highly relevant to OMS (Table 6). Glucocorticoids induce or suppress the transcription of many genes and messenger RNA (mRNA) translation (192). They affect immune cell numbers, phagocytosis, migration, antigen processing and presentation, and inflammatory responses (198). Until recently, it has been thought that the effects of ACTH on the immune system were mediated by

TABLE 6. *Effects of ACTH and corticosteroids on immune system in vitro*

Parameter	Reference
ACTH	
Reduced macrophage-mediated tumoricidal activity	203
Inhibition of antibody response to T-cell–dependent antigen	200
Suppression of the lymphokine IFN-γ response to mitogenic stimulation	201
Enhanced IgM secretion and H chain mRNA expression by B cells	204
Increased proliferation of activated B cells in presence of IL-2	202
No effect on NK- and IL-2–stimulated NK activity	205
Corticosteroids[a]	
Lymphocytopenia (especially T cells) through redistribution	
Decrased circulating monocytes and eosinophils through redistribution	
Decreased lymphocytic differentiation and proliferation	
Interference with lymphokine production or function (IL-2)	
Inhibition of macrophage function	
Inhibition of specific but not nonspecific antibody responses of B cells	

ACTH, adrenocorticotropic hormone; IFN, interferon; IgM, immunoglobulin M; mRNA, messenger RNA; IL, interleukin; NK, natural killer cells.
[a] References: 192, 199.

the release of corticosteroids (199). However, studies in vitro have demonstrated a wide range of components of the immune system that are modulated by ACTH. ACTH modulates B-cell proliferation and antibody production, T-cell–mediated defenses, mitogen-stimulated lymphokine production, and the capacity of macrophages to attack tumor cells (200–206). In structure activity studies, fragments of ACTH that do not stimulate steroid production were active in effects on the immune system, and because these studies were performed in vitro, corticosteroid production as a possible mechanism was eliminated. These studies do suggest direct effects of ACTH on the immune system. In contrast, ACTH increased NK cell cytotoxicity (NK and IL-2 stimulated) in vivo but not in vitro (205), implicating involvement of corticosteroids. Reciprocal feedback between the neuroendocrine and immune system has also been shown with the production, by leukocytes, of peptide hormones, including ACTH, and the presence of ACTH receptors on leukocytes (207–210).

Intravenous Immunoglobulins

Intravenous immunoglobulins are commercial preparations of IgG that have been obtained from plasma pools of thousands of healthy blood donors. Abbreviations for intravenous immunoglobulins are varied and include IVIG, IGIg, i.v.IG, IGIV, hIVIG (for human) or IVGG (for gammaglobulins).

Products

Most IVIG preparations contain only traces of IgA, IgM, and of Fc-dependent IgG aggregates; however, they do contain large amounts of intact IgG in a spectrum of subclasses found in normal serum (117). Obtained from a large number of donors, IVIG represents a full human IgG repertoire consisting of antibodies to external antigens, overreactive antibodies, and anti-antibodies. IVIG contains up to 30% of $F(ab')_2$-$F(ab')_2$ (fragments that lack Fc) dimers; however, there is a lack of standardized methods for quantification of antibodies. The differences in commercial preparations may be clinically important. One advantage of using a mixture of IgG subclasses found in IVIG is to provide wider antibody coverage.

There are at least nine commercially available forms of IVIG available worldwide, seven of which are licensed in the United States. These products differ in a variety of manufacturing processes, the starting materials, pH, use of additives, and stabilizers. It is advisable, before the use of IVIG products, to screen for IgA deficiency (211). Decreased IgA, which is common in autoimmune disease, may lead to the development of autoantibodies to IgA and result in a severe reaction to IVIG. It is best to use IgA-depleted products. It is also important to monitor for hepatitis non-A and non-B. Because IVIG is a blood product, contact with acquired immune deficiency virus is a rare possibility. Cytomegalovirus neutralization titers may vary between IVIG products, and there is also lot-to-lot variability even in the same commercial preparation. The choice of a product is important. If one IVIG treatment fails, a different IVIG product should be tried. IgA content is low (<30 μg/ml) except in Gamimune N (70 μg/ml) and Sandoglobulin (720

μg/ml). Osmolality is high in Gammagard and Polygam (~630 mOsm). The pH after reconstitution is near neutral except for Gamimune N and Venoglobulin-S.

Indications

Gammaglobulins have been administered to humans for many years and have been used safely even in infants (212). There have been several recent reviews of clinical uses of intravenous immunoglobulins (117,213–215). The main categories of use of IVIG are replacement therapy for primary and secondary immunodeficiency disorders or for immunomodulation (216). IVIG has been used to treat many different neurologic disorders including myasthenia gravis, Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy, monoclonal gammopathies, infantile spasms, adrenoleukodystrophy, and refractory polymyositis. There is a paucity of controlled trials to show efficacy and evaluate dosage regimens, however. The clinical reports have been unblinded, nonrandomized, and uncontrolled. Such is also the case for OMS syndrome.

The first published article on the use of IVIG in OMS described a severely affected 14-month-old boy with a postviral etiology who responded to 150 mg/kg/day of IVIG (Bayer) over 3 days but not to 2 mg/kg/day of prednisolone for 1 month (93). Improvement began 4 days after the first IVIG therapy. Opsoclonus, myoclonus, and irritability responded completely, but ataxia was still moderately severe 2 weeks after IVIG, and standing without support and walking alone were impossible. A 34-month-old girl with neuroblastoma-associated OMS, seizures, areflexia, progressive hearing loss, and tonic pupils was treated with 400 mg/kg/day for 4 days and 1 g/kg monthly for 1 year with improvement of OMS but not seizures, tonic pupils, and areflexia (88). She had previously been treated with prednisone after tumor resection and anti-Hu antibodies were found in serum and CSF even 1 year after IVIG and steroid treatments. Improvement was reported in five patients with postinfectious acute cerebellar ataxia with opsoclonus after IVIG treatment, with a longer delay in the onset of improvement (7–10 days) in three who had been treated previously with steroids compared to no steroids (1–3 days) (217). In this early phase of IVIG use in OMS, the results are probably biased upwards because of reporting of positive but not negative responses. In the experience of the National Pediatric Myoclonus Center, IVIG is a valuable treatment, but not all children respond.

In adults with paraneoplastic syndromes, IVIG may also be effective, but symptoms may progress relentlessly despite any treatment (218–220).

Adverse Reactions

The incidence of adverse effects associated with IVIG is estimated to be ~1 to 15% on the basis of manufacturer's information. The volume of IVIG given in the rate of infusion appear to be correlated with these side effects, most of which are mild and self-limited. In some cases, if reducing the rate of volume of infusion does not prevent side effects, the concomitant administration of hydrocortisone in a dose of 1–2 mg/kg intravenously has been given 30 min before IVIG infusion. If patients have a history of migraines, they may experience headaches during IVIG,

and rarely develop aseptic meningitis due to crossing of the blood–brain barrier by IVIG (increased IgG in CSF, sometimes with eosinophils). Although there has been a trend to favor the use of high-dose IVIG as more effective than low-dose, high-dose IVIG has more potential risks. It can increase blood viscosity related to the elevated IgG, and in the elderly has been associated with thromboembolic events (221,222), renal failure (223), aseptic meningitis (224,225), and other rare side effects (226). The long-term effect of IVIG on the immune system in OMS is unclear.

Pharmacokinetics

Intravenous infusion of immunoglobulins results in a rapid increase and also a rapid decrease in serum immunoglobulin levels. A dose of 100 mg/kg of body weight increases serum immunoglobulin level by ~200 mg/dl (227,228). A dose of 500 ml/dl results in an increment of approximately 1 g/dl (229). Doses of 150 mg/kg of body weight have been used in primary immune deficiency, and the superiority of higher doses is unsubstantiated. Twenty-four hours after IVIG infusions, serum immunoglobulin levels decrease to ~70–80% of peak levels, and by 72 h, they are ~50% of peak levels, followed by exponential decline (230,231). The half-life of IgG in vivo is ~3 weeks for IgG1, IgG2, and IgG4, although less for IgG3. As for native IgG, the range of half-lifes for IVIG is 18 to 32 days. The fate of intravenous immunoglobulins depends on factors such as metabolism of the denatured molecules, clearance of immune complexes formed after interactions with antigens, and extravascular redistribution. Infused immunoglobulins also undergo catabolism. It would appear that the pharmacokinetics in children is similar to that in adults. However, there is considerable individual variability. The causes of this variability are multifactorial and include the immunoglobulin levels before and after infusion, the nature of the condition being treated, measurement of immunoglobulins, and other factors.

Mechanism of Action

Although the mechanism of action of IVIG in any autoimmune disorders is unknown, there are several hypotheses (Table 7). These hypotheses may be overlapping and are not mutually exclusive (215). One hypothesis is that IVIG "jams the sensors" of immunocompetent cells. Specifically, the large excess of IgG provided in IVIG blockades the Fc-receptor component on the surface of reticular endothelial cells, phagocytic cells, and target cells, thereby inhibiting the destruction of autoantibody-bearing cells (120). The Fc receptor mediates cell destruction by providing a "foothold" on autoantibody-bound cells unless blocked by IVIG (232). Alternatively, IVIG may provide anti-idiotypic antibodies directed against circulating autoantibodies in OMS, increasing their clearance and downregulating their production (233,234). IVIG shares anti-idiotypic specificities against autoantibodies with heterologous anti-idiotypic antibodies (235). Anti-idiotypic antibodies bind to the variable region ("idiotype" is antigenic marker within variable region) of other antibodies and may be part of a regulatory network involved in suppressing pathologic antibody production. It is unclear if this would selectively

TABLE 7. *IVIG mechanisms of action* (hypotheses)*

Parameter	Reference
Antibody Fc receptor blockade on phagocytic cells	232
Anti-idiotypic antibodies against autoantibodies and idiotypic regulation of B- and T-cell function	233–235
Elimination of infectious agents by antimicrobial antibodies	214
Immunomodulation of T-cell subsets (increased T-suppressor cells and natural killer cells)	237, 238
Decreased autoantibody synthesis by B cells by feedback inhibition	239
Inhibition of lymphocyte proliferation	245
Impaired complement and immune complexes (inhibits C3 binding to target tissue)	240
Antibodies against superantigens and activated T cells	236, 241
Inhibition or modulation of interleukins and inflammatory mediators	241, 243
Soluble CD4, CD8, HL (DR, ABC)	238, 244
Neutralization of cytokine activity, blocking of cytokine receptors	241

IVIG, intravenous immunoglobulin.

target plasma cells or other B-lymphocyte lineage. A third possibility is that IVIG eliminates infectious agents because antiviral antibodies and other antimicrobial antibodies are found in these preparations. IVIG would thereby block the binding of antigens from virus or neuroblastoma to host cells and prevent the autoimmune response to the complex of neoantigen and cell (host cell) antigen (236). IVIG preparations contain high levels of antibodies to many viral pathogens and several different viral infections respond to treatment with IVIG: echovirus, Epstein–Barr virus, adenovirus, influenza and parainfluenza virus, and respiratory syncytial virus (214). Several other possible IVIG mechanisms have been proposed (215–223).

There are no data on the mechanism of IVIG in OMS. It may be relevant that IVIG does not rapidly or consistently reduce autoantibodies to the AChR in myasthenia gravis (224–226) or antiganglioside antibodies in motor neuropathy (218). To the extent that OMS is mediated by autoantibodies, low efficacy of IVIG in reducing autoantibodies may explain IVIG failures in OMS.

Therapeutic Apheresis

There are few reports of therapeutic apheresis in OMS. Plasma exchange is used in other immunologic disorders as a short-term measure to stabilize the patient. Besides plasma, blood cellular fractions may be removed selectively, such as leukocytes (leukapheresis, leukocytapheresis) or lymphocytes (lymphocytapheresis), using centriguation or membrane filtration techniques. One of the main limitations in pediatric cases is that the mean age, which is 18–24 months, is well below that in which plasmapheresis is technically feasible. Compared to IVIG, plasma exchange has the disadvantages that it reduces blood volume and may induce hypotension, is more immunosuppressive, removes plasma proteins, is less widely available, requires placement of a large-bore central venous catheter, and has more frequent and more serious side effects (227).

Plasmapheresis in adult-onset OMS is seldom successful despite reduction in antibody titers (68,194,228,229). In two adults with paraneoplastic encephalomy-

elitis and small-cell lung cancer and one patient with paraneoplastic cerebellar degeneration and ovarian cancer, plasmapheresis reduced the serum antibody titers to 20% of the initial levels, but CSF autoantibody titers decreased only in the patient with a compromised blood–brain barrier (193). This has been the case for other autoimmune disorders such as myasthenia gravis, in which antibody levels do not reflect disease severity or predict response to plasmapheresis (83). One boy with para/post infectious myoclonus (not OMS) responded to plasmapheresis (230).

Improvement in an adult with paraneoplastic OMS who harbored antoantibodies was reported after immunoadsorption (protein A column) therapy, although the patient died of metabolic disease (73). The mechanism of action of immunoadsorption with protein A (231) may include removal of autoantibodies and immune complexes or facilitation of anti-idiotype antibody formation (232).

Mechanism of Action

The physiology and mechanism of plasma exchange has been reviewed recently (227). One plasma exchange (~3 to 5 L of plasma removed) reduces plasma concentration of immunoglobulin, complement, and coagulation factors by ~60%, with three to five courses of plasma exchange reducing levels by >90% (233,234). Most plasma proteins return to 75% or more of prior levels within 2 days, whereas serum IgG levels may be reduced for several weeks (235). Removal of other immunologic plasma components, such as cytokines, could be important; however, the circulating half-lives of many cytokines are only a few hours (236).

It is likely that plasma exchange works mainly by removing pathogenic antibodies. The effect of plasmapheresis is relatively short lived, which is not a problem in monophasic illness, but the duration of immunologic dysfunction in OMS is not known. It has been suggested that plasmapheresis may augment the effect of cytotoxic immunosuppressive drugs by inducing lymphocytes to proliferate, making them more susceptible to drug action (237). However, antibody rebound after plasmapheresis may also occur (238) and theoretically may induce clonal expansion of antibody-producing cells. Rebound immunoglobulin production after plasma exchange may not be clinically significant in humans (239,240), but various strategies for suppressing rebound have been proposed, including the use of cytotoxic agents after plasma exchange (241,242). One difficulty in analyzing the pheresis literature is that there are many different types of pheresis, and what is removed varies depending on the method used (membrane filtration, continuous centrifigation, discontinuous centrifigation; 243). Sufficient detail is seldom reported. These differences may be important because, besides reducing antibodies, plasmapheresis may change lymphocyte subsets (244). The combination of plasmapheresis and chemotherapy may be effective (245). IVIG treatment could be combined with plasma exchange, providing synergy on theoretical grounds, but the optimal treatment schedule has not been devised (227).

Other Immunosuppressants

Chemotherapy is the predominant modality of management in neuroblastoma, although it would not be a routine part of treatment of low-risk disease such as

International Neuroblastoma Staging System stage 1 neuroblastoma (23). Although cancer chemotherapy has not been used in the treatment of OMS of presumed viral etiology, it has been part of the regimen in some paraneoplastic cases. The use of cancer chemotherapy has not been studied systematically in OMS. Cyclophosphamide has been used, alone or in combination with vincristine and other chemotherapy. More often, chemotherapy, radiation therapy, and surgical treatments are combined. It will be important to determine if chemotherapy should be used in all moderate to severe cases of OMS.

Cytotoxic agents such as cyclophosphamide, chlorambucil, and methotrexate are more powerful immunosuppressants, have more severe side effects, and are used when less toxic agents are ineffective (246) (Table 8). Well known in cancer chemotherapy, they are used also in autoimmune diseases. Methotrexate, an antimetabolite, is given intermittently orally or intravenously. Bone marrow depression and hepatotoxicity are side effects. Cyclophosphamide, an alkylating agent, preferentially suppresses B cells when given orally or intravenously in high doses. Serious side effects include malignancies (especially with total cumulative dose >85 g), bone marrow depression, sterility, hemorrhagic cystitis, and gastro-intestinal symptoms. It is recommended that cyclophosphamide be used intravenously only the better to control side effects and limit total dosage. Chlorambucil, another alkylating agent, has fewer but similar side effects compared with cyclophosphamide.

Cyclosporin A, a cyclic peptide derived from fungus, is used to prevent transplant rejection. It inhibits T-cell activation and production of soluble cell mediators such as IL-2 by $CD4^+$ T cells (247). Its limitations include erratic absorption, expense, nephrotoxicity, sequestration in body fat, and interaction with drugs

TABLE 8. *Immunopharmacology for autoimmune diseases[a]*

Immunosuppressants
  Noncytotoxic (ACTH, corticosteroids, cyclosporin A)
  Cytotoxic agents (azathioprine, cyclophosphamide, methotrexate)
Anti-lymphocyte therapy
  MoAbs (anti-CD3, anti-CD4, and anti-CD5, anti-IL-2P, anti-TCR)
  Lymphocytapheresis
  Thoracic-duct drainage
  Total lymphoid irradiation
Anti-MHC II therapy
Anti-cytokine therapy
  MoAbs to cytokines
  Soluble cytokine receptors
  Cytokine inhibitors (IL-1 ra)
Antiidiotypic Igs
Peripheral tolerance (oral autoantigens)
Biological response modifiers (BRMs)
  Cytokines
  Thymic hormones
  Chemicals (levamisole, bestatin, lobenzarit, inosine pronobex, diethyldithiocarbamate, tuftsin, imuthiol)
Antiinflammatory drugs (steroids, NSAIDs)

NSAID, nonsteroidal antiinflammatory drugs; ACTH, adrenocorticotropic hormone; MHC, major histocompatability complex; MoAb, monoclonal antibody; IL, interleukin; Ig, immunoglobulin.
[a] References: 282–284.

such as steroids. Unlike cytotoxic immunosuppressants, cyclosporine does not cause myelosuppression.

Azathioprine, a purine analog or prodrug metabolized to 6-mercaptopurine, is useful in T cell—dependent antibody-mediated disorders. Although it is one of the easiest immunosuppressive agents to use, ~10% of patients treated will develop an idiosyncratic flu-like reaction, precluding its use.

Possible Future Therapies

Before considering new therapies, the need for regimens of combination therapy using currently available immunomodulatory drugs should be emphasized. They allow steroid sparing, targeting of multiple immunologic effector pathways, and provide a mixture of early- and late-acting drugs for acute and subchronic treatment. Modifications of conventional agents may also improve treatment. Defloxacort is a new steroid purported to have fewer side effects.

Identification of the trigger autoantigen and specific immunologic defect in OMS would open the possibility of new therapeutic approaches. Therapies used in other autoimmune diseases (248–250), the opposite of adoptive immunotherapeutic approaches to cancer (175,251,252), provide examples: therapy directed against cytokines (anti-cytokine monoclonal antibodies, soluble cytokine receptor proteins, specific cytokine antagonists or inhibitors), anti-idiotypic immunoglobulins, therapy directed against T cells (lymphocytapheresis, cyclosporin A, monoclonal antibodies to lymphocyte receptors; 253,254). Total lymphoid irradiation is immunosuppressive and may reinduce tolerance to antigens present at the time of treatment. Specific immunotherapies include anti-MHC class II therapy (to interrupt the formation of the MHC, TCR, and antigen triad), anti–T-cell receptor (which may eliminate pathogenic T cells from circulation) and T-cell vaccination, and antigen-driven peripheral tolerance (such as by oral administration of the antigen) (255–257). The technique of engineering "humanized" antibodies for antibody-based therapy is also promising (258). Immunogenetherapy can be applied to cytokines and other immune mediators (259). These exciting possibilities for the treatment of OMS should serve to stimulate further research efforts.

New immunosuppressive drugs are promising (260–262). FK506, a macrolide antibiotic, selectively inhibits CD4$^+$ T-cell activation and cytokine production before T-cell activation (263). It can be used with cyclosporin. Another macrolide antibiotic, rapamycin, inhibits T- and B-cell proliferation, even after T-cell activation, induces clonal deletion, and inhibits IL-2 production by T cells. The antipurine metabolite, RS 61443, a mycophenolic acid derivative, acts on B and T cells. Anti-adhesion molecules ELAM-1, ICAM-1, and ICAM-2, and monoclonal antibodies against TCR, IL-2R, TNF-α, CD3, and CD4 are available. Many immunostimulators/modulators, or biological response modifiers (BMRs), are being tested (259,262).

CONCLUSIONS

The immunological theory of OMS is supported by many different lines of evidence and reasoning, which makes OMS an important conceptual part of the

spectrum of putative autoimmune neurologic disorders. An abnormality of both humoral and cellular immunity (i.e., both B cells and T cells) is the most attractive hypothesis based on current data available in OMS and abundant information on other autoimmune neurologic disorders. A peripheral induction mechanism involving molecular mimicry or one of several other possible mechanisms leads to immune system dysregulation, which transiently allows otherwise forbidden autoaggression against cross-reactive brain antigens. Although immunizations are logical candidates for costimulation in peripheral induction in children, if there is an adult counterpart, it is unknown. The targets of brain injury currently identified are neuronal and cerebellar, but possible involvement of glia and other brain regions in some clinical subgroups should not be overlooked. The cellular and subcellular targets appear to be selective, discrete, and not widespread, and the injury may be sublethal or lethal depending on several variables.

Current immunotherapy is more effective in pediatric than in adult cases of OMS for reasons that are not understood, but also may fail in children to deliver the sufficient antiimmune force soon enough to prevent permanent neurologic sequelae. Because some children respond well to minimal treatment, there has been the misperception that aggressive immunotherapy is not necessary in severe cases. Failure of current therapies in some patients with the same phenotype as drug responders underlines the complexity of immune system regulation. The myriad immunologic effects of therapies such as ACTH, corticosteroids, IVIG, and apheresis emphasize the complexity of immunoregulation and the multiple points at which the system can be regulated; therefore, some treatments are likely to be synergistic. The capacity of IVIG, which is not a general immunosuppressant, to be efficacious in some patients makes a case for therapeutic strategies for immunomodulation. Nuances in the afferent and efferent pathways of the immunologic response in OMS provide multiple potential targets for therapeutic intervention. Little attention has been focused on differences in patients' capacity for immune system reregulation after the onset of OMS, which probably plays a role in the heterogeneity of clinical phenotypes, severity of neurologic involvement, and outcome of OMS. Clinical and immunologic age-related differences in OMS provide important but unexplained clues to pathophysiology, including possible age-related differences in the immune system. New potential immunotherapies have practical and theoretical advantages to general immunosuppressants but require more information about the specific immunologic defect in OMS for rational use. There is every reason to believe that the available data are only the "tip of the iceberg" in OMS. Both further basic research and clinical trials are needed in OMS.

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