Struggling with Rasmussen's Syndrome

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Rasmussen's syndrome has remained an enigma since it was first described as a clinical and pathological entity in 1958. Determining the etiology and how best to treat the condition has been an enduring struggle for clinicians, pathologists, surgeons, neuroscientists, and above all, for the families who need to make treatment decisions for their children. Bien and colleagues capture the tension of this struggle in an excellent, recently published review that provides the basis for the European consensus statement (1).

Frustration with understanding Rasmussen's syndrome begins with efforts to determine the cause of this devastating disorder, which can destroy a cerebral hemisphere in previously normal children. When the pathologic findings were first noted (lymphocytic infiltration and microglial nodules), it was assumed that a viral etiology would shortly be discovered. This line of investigation was avidly pursued, with increasingly sophisticated methodology, until about a decade ago. No consistently reliable viral cause has been found. The next wave of enthusiasm in determining the etiology focused on the report of elevated GluR3 antibodies (2) in some patients with Rasmussen's syndrome and improvements that were seen when patients underwent plasmapheresis (3). Theories were postulated to explain how these circulating antibodies were responsible for unihemispheric abnormalities. For example, one hypothesis suggested that a localized dysfunction (e.g., trauma, infection, etc.) led to a breakdown of the blood–brain barrier, which then allowed the GluR3 antibodies to attack neurons—either through cytotoxic activation of the glutamate receptor or through complement activation. However, elevated GluR3 antibodies have been found in other types of seizure disorders, and certainly they are not found in all patients with Rasmussen's syndrome. Interest continues in pursuing other humoral-related mechanisms, but in the last decade, the focus of much research has shifted to examining the role of T-cell–mediated toxicity. This line of investigation is fueled by the recognition that the vast majority of inflammatory cells involved in Rasmussen's syndrome are T cells; in fact, they are cytotoxic $CD8^+$ lymphocytes, which have been shown to attack neurons.

The pathologic findings underscore the problems associated with understanding the cause of Rasmussen's syndrome. Abnormal and normal tissue can be found in juxtaposition to each other. What is the pathogenesis that can cause regions of multifocal destruction to be surrounded by normal appearing tissue? This feature of Rasmussen's syndrome leads to a sense of futility for performing brain biopsies, and it also forces consideration of mechanisms postulated for multiple sclerosis and postinfectious encephalomyelitis (4).

The clinical manifestations of Rasmussen's syndrome are often confusing. Although the hallmark of the disease is epilepsia partialis continua, it does not occur in all patients and the nature of the focal seizures is very unusual. While the progression of partial seizures is usually envisioned as a Jacksonian march, this image is routinely not the case in Rasmussen's syndrome. Clonic activity may begin in the face; then in the hand, then the leg, and then the shoulder—the progression obviously reflects the patchy nature of the hemispheric pathology. Children also can manifest features of a movement disorder before seizures are clearly apparent. The EEG often is confusing. It may show a paucity of epileptiform activity, even with epilepsia partialis continua. Bilateral abnormalities are not uncommon. MRI has become one of the most important tools to confirm the presence of Rasmussen's syndrome. Atrophy, particularly progressive atrophy, will appear. This feature, too, does not always reflect the clinical situation. Extensive atrophy has been noted at clinical onset in some children while other children show minimal change for varying periods of time. Clinical and MRI progression of the disease is quite variable. Disease progression can happen quickly with devastating results, and it can happen insidiously, with periods of respite that circumvent more definitive treatments. The European consensus group devotes a long table to elaborating the differential diagnosis of Rasmussen's syndrome; however, close inspection of the list reveals that the critical aspects of diagnosis are the history, EEG, and MRI (1). There is no test that is specific for Rasmussen's syndrome, even biopsy.

Medical treatment of Rasmussen's syndrome has largely been a failure. Standard anticonvulsant therapy does not stop

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the seizures. There has been more than a decade of experience in using various forms of immunotherapy, but these are unsatisfactory as well. Corticosteroids are probably effective in the short-term and when status epilepticus is present. Long-term use is problematic. Intravenous immunoglobulin replacement therapy may stabilize patients for varying periods of time and has been used in combination with steroids for some individuals. Side effects, including aseptic meningitis and phlebitis, exist, and the cost of treatment is not inconsequential. Plasmapheresis was popular when GluR3 antibodies were believed to be the etiologic factor but does not appear to be effective for long-term use. Newer forms of immunomodulation are hopeful, including one described in an earlier report by Bien et al. (5) on the use of tacrolimus to stabilize neurological function and prevent further atrophy (without improved seizure control). In addition, preliminary work using immunoablation with cyclophosphamide to eliminate the T-cell population that apparently is activated and then destroying brain seems promising (6). Following cyclophosphamide treatment, the lymphocytes that subsequently are generated presumably are naïve and would not continue the destruction of brain.

Surgery also has been part of the artillery used to battle Rasmussen's syndrome. In the earliest days it became clear that the entire hemisphere had to be removed to produce a cure. However, in the 1960s and early 1970s, there was virtually a moratorium on using surgery because of concerns about long-term problems, such as hemosiderosis. The moratorium ended when better techniques, as well as neuroimaging, became available in the late 1970s and early 1980s. Surgeons continue to search to define the best technique, with variations that include hemidecorticectomy and hemispherotomy with disconnection.

Proposed diagnostic criteria are at the heart of the consensus statement paper by Bien et al., and they convey a sensitivity to properly diagnosing patients before extensive tissue destruction has occurred (1). Early diagnosis is important to avoid the only cure currently available—removal of the hemisphere. If caught early, before the process destroys much of the hemisphere, the child might have seizures that could be controlled with medication, without the significant handicap of a hemiplegia. Although previous attempts to establish diagnostic criteria have failed, the consensus reached by the European group is significant. According to their statement, diagnosis is achieved in one of two ways (1). First, a diagnosis is reliably made when all three criteria found in Part A of the consensus statement are fulfilled: (i) focal seizures with unilateral cortical deficit; (ii) EEG showing unihemispheric slowing (± epileptiform activity), with unilateral seizure onset; and (iii) MRI, with unihemispheric focal cortical atrophy and either grey or white matter T2/FLAIR hyperintense signal or by changes in the ipsilateral caudate head. Second, diagnosis is attained if two out of three of the features in Part B are fulfilled: (i) epilepsia partialis continua or progressive unilateral cortical deficit, (ii) progressive unihemispheric focal cortical atrophy on MRI, or (iii) appropriate histopathology on biopsy. Using these criteria, the majority of individuals can be diagnosed without biopsy.

The ultimate frustration in coping with Rasmussen's syndrome lies in the failure to be able to effectively treat this obviously immune-mediated disease. The European consensus group has provided a thoughtful algorithm for the therapeutic approach to patients with Rasmussen's syndrome (1). The algorithm appropriately considers the seizures as well as the progressive neurologic decline that accompanies the disease—both of which clearly should influence decisions regarding therapy. Although the authors describe patients with ongoing progression of neurologic dysfunction, who do not have intractable seizures and can be referred for continuing immunotherapy, this scenario is virtually unknown. The consensus group also provided a list of recommended areas for future therapeutic research, which is admirable. The group recognizes the difficulties in studying this population, particularly in regard to efficacy parameters.

A few final thoughts about the struggle: parents and patients engage in a particularly difficult process, as the affected children were normal before this insidious process began. Parents are looking for a cure that will halt the progression and return their child to previous functional levels. Anticonvulsants and hemispherectomy cannot achieve this result. And so far, immunotherapy has not been effective. Early diagnosis is critical—before significant neurological deterioration and destruction of the brain occurs. And finally, greater understanding of the etiology of Rasmussen's syndrome is essential to the ability to determine specific therapies.

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