COMMENTARIES

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Magnetoencephalographic Patterns of Epileptiform Activity in Children With Regressive Autism Spectrum Disorders

ABBREVIATION. EEG, electroencephalogram.

The issue of the contribution of subclinical epilepsy to autistic spectrum and developmental and acquired communication and language disorders is one of the most important in clinical developmental neurosciences. We need to know what proportion of these disorders are caused or triggered by epilepsy, to what extent can the process be reversed and what would be the mechanism of such catastrophic selective and global loss of cortical function. The model that has been used in the study reported by Lewine and colleagues in this month’s issue is of a disorder that has an onset after a period of normal or near normal early development and their finding of evidence of seizure activity in the majority of these children has to be taken seriously. A recently published French study found a rate of 50% of epileptiform electroencephalogram (EEG) activity in sleep in primary developmental dysphasia and this opens the question more widely to include both non regressive and pure language disorders.

The authors have separated what they call “classical Landau-Kleffner syndrome” from variants by the presence of wider impairments. However, we should remember that Landau and Kleffner included patients with wider behavioral impairments in their original description.

The main value of the study is to add further evidence to that of the Helsinki group that magnetoencephalography probably has a greater yield than traditional sleep recorded EEG and certainly from a short waking record and that this appears to be related to the electrical characteristics of discharges arising in the Sylvian fissure.

Most of the problems of studies in this admittedly difficult area are illustrated by this publication.

Received for publication Mar 29, 1999; accepted Mar 29, 1999.
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The criteria for entry into the study and source of the patients is not given so that no prevalence inference can be made. Perhaps more importantly patients may have been externally or even internally selected for having an epileptic EEG.

DELAY BETWEEN ENCEPHALOPATHY (ACUTE DETERIORATION) AND STUDY

This is a problem with most studies and could only be approached by population screening along the lines of the Checklist for Autism in Toddlers (CHAT) study.

THE LACK OF MULTIDOMAIN ASSESSMENT TOOLS

The article’s analysis of the published data does not draw attention to the lack of appropriate assessment tools in both the corticosteroid studies and even the much quoted multiple subpial transection paper. In that latter study it is difficult to accept the assertion that language returned to age-appropriate levels in many without the data on language function being quoted. This problem is not fully dealt with in the preliminary report of their surgically treated patients where the outcomes are the Peabody Picture Vocabulary Test, which assesses one domain, and the Childhood Autism Rating Scale, which is mainly an ascertainment tool plus clinical observations. These preliminary results show, as have others, that improvements can be seen by intensive treatment, including surgical, of children with autistic spectrum disorders and clinical or subclinical epilepsy. The need for controlled studies with good assessment tools is becoming a matter of urgency because of the high rate of autistic spectrum disorders in the community, their poor prognosis, and the understandable demands of families for the epilepsy stone to be turned.
RSV Immune Globulin Prophylaxis: Is an Ounce of Prevention Worth a Pound of Cure?

In this issue of Pediatrics, Joffe et al reported limited cost-effectiveness of the immune globulin products (RSV-IGIV [Respigam] or palivizumab [Synagis]) to prevent RSV hospitalization. Several assumptions strongly favoring immune globulin prophylaxis were used in their analyses. The authors concluded that current AAP recommendations regarding RSV immune globulin products may be too broad because a lack of cost-effectiveness observed. In only 1 of the 8 subgroup analyses (Group A infants with gestation <32 weeks, oxygen requirement 28 days, neonatal intensive care unit discharge between September and November, and prophylaxis with palivizumab), was cost-effectiveness in terms of cost per life-year saved and cost to avoid hospitalization seemingly approached.

It is important in cost-effectiveness studies for reviewers and readers to carefully consider assumptions made because results may be profoundly affected. To their credit, the authors carefully acknowledged intentionally biasing their assumptions in the direction of benefiting the immune globulin therapies. For example, one assumption made was that only 4 doses of a RSV immune globulin preparation would be necessary to prevent RSV disease each season. In previous efficacy studies, 5 doses were generally administered. The authors assumed that efficacy would not have been altered by such a decision. This resulted in a 20% reduction in drug cost and administration-related costs for prophylaxis, but a larger proportional reduction in the cost to avoid a RSV hospitalization. Had 5 palivizumab doses been assumed to be required in the most cost-effective scenario (Group A), costs per hospital admission avoided would have increased from $12,000 to over $17,000 (>40%) and costs per year of life saved increased from $33,000 to $48,110 (>45%). Additionally, it was assumed that no drug wastage occurs; a condition unlikely to be met in actual practice. Finally, efficacy from randomized clinical trial reports was used as a measure of effectiveness in actual clinical practice. When products are used outside clinical trials, effectiveness may be reduced because ideal study conditions no longer exist (timely dosing, education concerning avoidance of exposure to high-risk settings, etc). Despite these major assumptions favorable to active prophylaxis, the authors conclude immune globulin products do not appear cost-effective for most subgroups.

The authors make one major assumption related to cost-effectiveness of RSV immune globulin therapies, upon which other major findings of their report depend and which may not be justified. This assumption is that mortality of RSV correlates directly with hospital admission rate rather than treatment status. Because immune globulin prophylaxis reduces hospitalization by about 50%, this would result in a major increase in the mortality risk for the no prophylaxis control group at a ratio of about 2:1 compared with the actively treated group. This critical assumption is not supported in the literature but has been made before. In the three randomized clinical trials from which the authors derived the 1.2% pooled mortality estimate for RSV hospitalization, there were 2 deaths in 173 hospitalized RSV patients described. However, both hospital deaths occurred in patients receiving previous prophylaxis rather than control patients. Concern of increased morbidity or trends for increased mortality associated with immune globulin prophylaxis has been observed in patients with congenital heart disease and has resulted in recommendations against immune globulin prophylaxis in select patients. (Had the authors assumed that death occurred only in patients receiving immune globulin, the analysis would be highly against immune globulin administration because of increased mortality and increased cost). The authors artificially created a twofold increase in mortality in the no treatment group, which has no valid basis. Without this assumption, there exists no life-years saved and no cost per life-year saved to be reported for either of the RSV immune globulin products.

In this reviewer’s opinion, expert committees responsible for recommendations related to expensive therapeutic agents will need to become more proactive in the future and not bypass cost-effectiveness issues when publishing practice guidelines. Because of limited health care resources, expert committees must make their best estimate of cost-effectiveness when ideal data are not available. The time lag until well-designed generalizable postmarketing studies are published may be several years. In the meantime, costs will be simply set by those most likely to benefit (eg, a pharmaceutical company). It may be to a company’s advantage under some circumstances not to sponsor well-conceived generalizable phase IV postmarketing cost-effectiveness studies. Unfortunately, the Food and Drug Administration does not assess agents for cost-effectiveness before approval and the long, rigorous funding process through agencies such as the National Institutes of Health or the Agency for Health Care Policy Research would result in long delays to eventual study publication.

At this time, there is no evidence that RSV immune globulin products improve RSV mortality resulting in years of life saved at any cost. Other reports also suggest that immune globulin products to prevent RSV hospitalization are too highly priced, based on currently available information regarding benefits actually observed. Further research is needed to define patient groups likely to have acceptable cost-
effectiveness resulting from RSV immune globulin administration. Research into potentially less expensive educational methods to prevent RSV infection should also be performed. Expert committees may need to update existing immune globulin recommendations. A recommendation for major cost reduction in these products and additional phase IV postmarketing effectiveness research seems appropriate. In the case of RSV immune globulin products, “an ounce of prevention” does not result “in a pound of cure” based on currently available information.

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*Pediatrics* 1999;104;559

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