Departments of [1]Neurology and [2]Pathology, Albany Medical Center; [3]Department of Pathology, St. Peter's Bender Laboratory; and [4]Genomics Institute, New York State Department of Health Wadsworth Center, Albany, NY

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Intravenous Immunoglobulin Response and Evidence for Pathogenic Antibodies in a Case of Complex Regional Pain Syndrome 1

Andreas Goebel, MD,[1,2] Michael Stock,[1,3] Rob Deacon, DPhil,[4] Guenter Sprotte, MD,[3] and Angela Vincent, FRCPath[1]

Immune factors have been implicated in chronic pain,[1] and patients with complex regional pain syndrome (CRPS) appear to respond to intravenous immunoglobulins (IVIGs).[2] A woman with CRPS1 recorded more than 50% pain reduction, accompanied by cessation of autonomic signs (without reversal of digital hypoaesthesia), during each 6 weeks after three IVIG treatments (Fig, A, $p < 0.0002$, comparing with the preceding 6 weeks). To look for possible pathogenic serum factors, we obtained serum samples just before two treatments (see Fig, A), and injected serum, IgG, or non-IgG fractions into C57Bl6 mice for 2 to 5 days, compared with serum or IgG from healthy individuals.

All mice behaved normally in their cages. There was no weight loss. However, after two daily injections, mice treated only with CRPS serum showed normal behavior in open-field exploration for about 30 seconds; after that most stopped moving, their bodies arched, piloerection was noted, and some appeared to shiver (changes clearly evident to blinded observers, and not observed previously with other disease or control sera). Over the 3-minute observation periods, rearing was decreased in the test mice at day 2 and day 8, but normalized by day 15 (see Fig B). Burrowing activity[3] was also significantly reduced ($p = 0.03$; data not shown), but there were no differences in motor strength or coordination. Overall, in three separate experiments (total 60 test mice, data not shown) with injection of either CRPS1 serum sample, there was abnormal physical behavior in open-field exploration by day 2 and a significant reduction in rearing ($p < 0.001$). Purified IgG also resulted in reduced rearing ($p < 0.05$), whereas the non-IgG fraction did not (data not shown).

CRPS is associated with changes to autonomic, sensory, and often motor components of the peripheral and central nervous systems, but the cause is unknown.[1] A role for macrophages and mast cells in the peripheral nervous system has been suggested,[1] and central neuroimmune activation and neuroinflammation has been described in rodent models of peripheral nerve trauma[4]; yet, little is known about other immune factors. The reproducible responses of this patient to IVIG treatments suggest that immune factors cause or contribute to her symptoms. Reduced explorative behavior has been correlated with pain in rodent models[5]; thus, the reduced rearing after injection of her serum or IgG supports a causative role of IgG antibodies. Our results should stimulate a search for pathogenic serum factors in CRPS and other pain disorders.

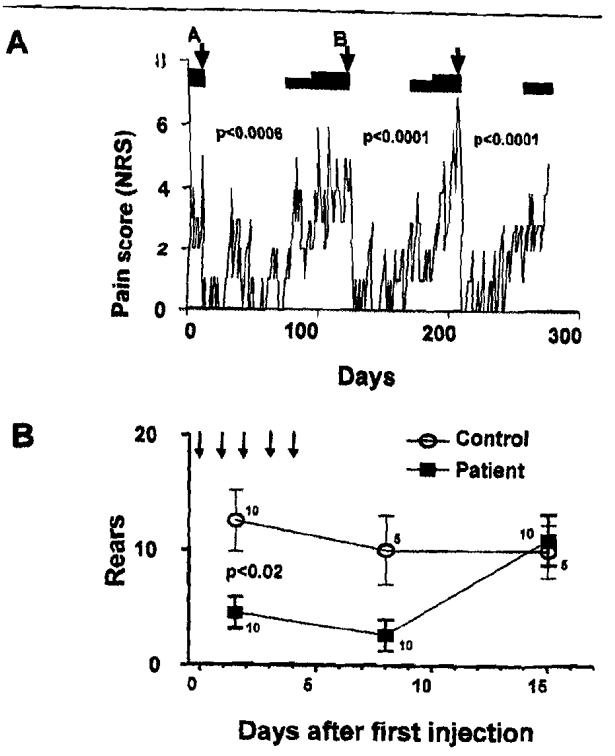

Fig. (A) The 36-year-old woman with complex regional pain syndrome (CRPS) had a painful right hand, with swelling, discoloration, and intense pain, disproportionate to a strain injury 2 years before. A guanethidine regional block had no effect, and stronger opioids and amitriptyline were badly tolerated. Pain diary scores were recorded on an 11-point (0–10) numeric rating scale (NRS). Horizontal bars indicate number of oral tramadol (100mg; thin bars, *one tablet;* thick bars, *two tablets) taken; there were no other treatments given. Bloods for serum and IgG preparation were taken, with institutional review board approval, at points A and B, just before IVIG treatments* (arrows, *3 × 10gm). (B) Passive transfer to mice. The graph illustrates results from the first experiment on 10 test and 10 control mice. Mice were injected for 5 days* (arrows) *with CRPS serum, sample A, and tested in open-field exploration on days 2, 8, and 15. The number of rears is shown. Small digits denote the number of mice tested (because of an error in the injection schedule at day 4, only five control mice remained thereafter).*

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[1]Neurosciences Group, Weatherall Institute of Molecular Medicine, University of Oxford, John Radcliffe Hospital; [2]Nuffield Department of Anaesthetics, University of Oxford, Oxford, United Kingdom; [3]Klinik fuer Anaesthesiologie, Schmerzambulanz, Universität Würzburg, Würzburg, Germany; and [4]Department of Experimental Psychology, University of Oxford, Oxford, United Kingdom

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Genetic Influence on Rolandic Epilepsy

Bhavna Bali, MD,[1] Steven L. Kugler, MD,[2] and Deb K. Pal, PhD, MRCP[1,3]

Vadlamudi and colleagues highlight the striking lack of concordance in cotwins of rolandic epilepsy (RE) individuals.[1] However, their failure to demonstrate trait concordance is inconsistent with all published twin studies (cited in Doose[2]), and with elevated sibling risks found in 10 family studies[2] (others cited in Luders[3]). Rather than evidence for absence of genetic influence, their negative finding can best be explained by measurement error and a too narrow definition of phenotype.

Misclassification

First, centrotemporal spikes (CTSs) are rarely detected after the age of 15 years; however, four of their eight cotwins were older than 15 years, reducing their sample to four twin-pairs. Second, CTSs are often exclusive to sleep, and sleep greatly increases their detection. Using 1-hour, sleep-deprived recordings, we found focal sharp waves in 8 of 12 (75%) siblings aged 5 to 15 years, from eight families of typical RE probands (B. Bali, L. Strug, L. Kull, D.K. Pal, unpublished). However, in the authors' report, only one of the four cotwins younger than 16 years had a sleep electroencephalogram recording, and this is another obvious reason for the underestimation of trait concordance.

Trait Choice

CTS, by definition, is a component trait in RE, but other associated traits may be just as crucial to take into account for genetic analysis. In RE, disorders of speech, language, and reading ability all show strong association. Scheffer and colleagues implied a possible common causative basis for speech dyspraxia and an autosomal dominant form of RE.[4] Our data also indicate comorbidity of reading or speech impairments in 13 of 24 (56%) of probands with typical RE, and aggregation of reading/speech impairments in 13 of 32 (40%) of their nonepileptic siblings. Including reading and speech impairments as component traits may significantly increase estimates of presumed genetic influence in RE.

Is Rolandic Epilepsy "Genetic"?

The relevance of concordance estimates for complex disease genetics is uncertain, given that susceptibility genes have been found in disorders (eg, narcolepsy, Rett's syndrome) that are not predicted by twin studies to have a strong genetic component. Moreover, although Vadlamudi and colleagues question an inherited basis for RE, they fail to mention evidence for a major gene effect for CTSs at a locus on chromosome 15q with heterogeneity.[5] Thus, the overwhelming weight of twin, family, and linkage studies suggests a strong genetic basis for CTS. We welcome Vadlamudi's contribution as an opportunity to air some of the important methodological issues facing complex disease researchers but caution readers that absence of evidence is not evidence of absence.

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[1]Department of Epidemiology, Columbia University, New York, NY; [2]Division of Child Neurology, Robert Wood Johnson Medical School, New Brunswick, NJ; and [3]Department of Psychiatry, Columbia University, New York, NY

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