Bilateral human fetal striatal transplantation in Huntington's disease

To the Editor: Referring to our report, “Bilateral human fetal striatal transplantation in Huntington’s disease,” Greenamyre and Shoulson suggest that we concluded that “a lack of significant worsening might reflect clinical benefit in a progressive neurodegenerative disease” and state that “this conclusion is a stretch.” However, regarding our study, we indicated that “we did not definitively demonstrate a lack of significant worsening owing to the small number of subjects and the open label design of the study. We also cannot exclude the influence of random chance, bias, or placebo effects.” Our study was intended to evaluate feasibility and safety, and was not designed to definitively assess efficacy. We concluded that transplantation of human fetal striatal cells is feasible and survival of transplanted cells was demonstrated, but patients with moderately advanced Huntington’s disease are at risk for subdural hemorrhage after transplantation surgery. We believe that our published manuscript provides a fair and balanced description of our observations and agree with the editorialists that we need better treatments for this devastating disease.

Robert A. Hauser, MD, Paul R. Sandberg, PhD, DSc, Thomas B. Freeman, MD, FACS, Tampa, FL; A. John Stoessl, MD, FRCP(C), Vancouver, BC, Canada

Older people with impaired mobility have specific loci of periventricular abnormality on MRI

To the Editor: I read the article by Benson et al.1 with interest. My own data, based on CT imaging, support their conclusions. In a convenience sample of 343 patients, including patients with stroke, gait was examined with a standardized scale2 and leukoaraiosis rated in seven brain regions using a modification of the van Swieten method.3 Neurologic abnormalities were quantified using the NIH Stroke Scale and supplemental scale. The brain region most correlated with gait disturbance was identified by analysis of variance. Ordered logit models were then used for further analysis (because of the ordinal nature of the gait scale).

The patients were predominantly men (96%) with a mean age of 68 ± 10 years. Leukoaraiosis was found in 160 patients (47%). A history of stroke was present in 179 patients (52%), and radiologic evidence of stroke was present in 176 (51%). Leukoaraiosis correlated with the presence of subcortical stroke (64% vs 37%, p = 0.001), but not with cortical stroke (47% vs 47%).

Analysis of variance found leukoaraiosis in the left frontal region had the highest correlation coefficient with the gait scale (r = 0.49, p < 0.0001; ordered logit coefficient 1.35, p < 0.001). In the absence of left frontal leukoaraiosis, no other region showed statistical correlation with the gait scale (coefficients ranged from −0.13 to 0.19, p = NS). Both a history of stroke (coefficient 1.06, p < 0.001) and radiologic evidence of stroke (particularly subcortical stroke: coefficient 0.73, p < 0.001) correlated with gait disturbance. Leg weakness or ataxia correlated with gait disturbance but not with left frontal leukoaraiosis. In models including all of the above, only leg weakness and ataxia (coefficient 1.56, p < 0.001) and left frontal leukoaraiosis (coefficient 1.32, p < 0.001) were independent predictors of gait disturbance.

Thus, these data support the role of frontal white matter leukoaraiosis, particularly on the left side, as a necessary lesion in gait disturbance, but not more posterior leukoaraiosis. This may reflect either different methodology or the larger number of patients examined. Perhaps the specificity that Benson et al.1 report with posterior leukoaraiosis reflects greater disease severity. Although leukoaraiosis does appear to be a form of cerebrovascular disease,3 my data indicate the effects are independent of those of overt stroke. I agree that leukoaraiosis may be associated with a “significant portion of mobility impairment” in older individuals and that further natural history studies are necessary as this may portend a poor prognosis.5

Acknowledgment

The author thanks Susan Sergent, PA-C, for data collection; Stuart Thomas, PhD, for data analysis; and his patients at the Huntington Veterans Affairs Medical Center, WV.

Dennis Briley, Oxford, UK

Randomized controlled trial of zonisamide for the treatment of partial-onset seizures

To the Editor: The article by Faught et al.1 is exciting news for epileptologists. However, the authors’ work raises several questions. Their Methods section does not mention prior or concurrent treatment of the patients’ seizures or other concurrent disorders. Did zonisamide affect blood levels of concurrent anticonvulsant medications, such as carbamazepine, or other agents such as digoxin? Did other medications affect zonisamide levels or half-lives? Drug–drug interactions are important treatment considerations. Was zonisamide more effective in combination with any other antiepileptic drug (AED)? Not all partial-onset seizures are the same—was there any difference in response with any particular

Correspondence

Reply from the Editorialists: It is unfortunate that we did not have the opportunity to see the final accepted version of the report by Hauser et al.1 who apparently took the reviewers’ comments to heart and toned down their original conclusion, which we called “a stretch.” We agree with Hauser et al.1 that the final published version presents a more balanced description of their results.

J. Timothy Greenamyre, MD, PhD, Atlanta, GA; Ira Shoulson, MD, Rochester, NY

Editor’s Note: Inadvertently, the Neurology office did not send the final accepted version of the Hauser et al. paper to Drs. Greenamyre and Shoulson. Thus their editorial criticized statements that were no longer part of the published article.1

We apologize to Hauser et al.1 and to Drs. Greenamyre and Shoulson for the error.

Robert C. Griggs, MD, Editor-in-Chief

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References


2. Greenamyre JT, Shoulson I. We need something better, and we need it now: fetal striatal transplantation in Huntington’s disease? Neurology 2002;58:675–676.

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Editor-in-Chief

Dennis Briley, Oxford, UK

References


underlying pathology or EEG finding? Zonisamide should be an important addition to our antiseizure arsenal.

Fred D. Haruda, MD, Albany, OR

Reply from the Authors: We appreciate Dr. Haruda’s comments and agree that knowledge of drug interactions is critical for the proper use of AED. Because of the many permutations of baseline AED regimens among patients, an additive therapy efficacy trial of this type is not well suited to quantification of drug interactions or to the stratification of which combination will work best. There were more than 20 different concomitant medication regimens in use, so insufficient numbers of each were available for meaningful comparison. Although we measured concomitant AED levels throughout this study, the results have not been analyzed. This was done primarily to aid treating physicians in the event of problems such as unexpected seizure increases or toxicity, in which case the data could have been accessed if necessary for emergency patient care. Most patients were taking carbamazepine or phenytoin alone or in combination with other drugs, and there were no identified adverse events related to changes in serum levels of AED.

Data from formal pharmacokinetic studies of zonisamide suggest that zonisamide clearance is increased and serum half-life decreased by about 50% in the presence of hepatic enzyme-inducing agents such as phenobarbital, carbamazepine, and phenytoin.2,3 Although this results in a lower serum zonisamide concentration for a given steady-state dose, no change in the once-daily zonisamide-dosing interval is necessary because the serum half-life—even in the presence of inducers—remains well above 24 hours.

Zonisamide has little effect upon the serum levels of other AED. There are conflicting reports of effects upon carbamazepine concentrations,4 but the effects, if any, are small and unlikely to be of clinical significance.

No differences in response related to pathology were observed.

Edward Faught, MD, Birmingham, AL; Ilo Leppik, MD, Minneapolis, MN; for the Zonisamide 922 Study Group

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References

Chronic ischemic monomelic neuropathy from critical limb ischemia

To the Editor: We read with great interest the recent article by Weinberg et al.1 reporting the clinical and electrophysiologic features of neuropathy due to chronic and critical arterial leg ischemia. These authors showed that reduced amplitude of sensory potentials, and especially compound muscle action potentials (CMAP), was far more frequent than previously reported, and they suggested that “regional neuropathy was commonly associated with chronic and critical leg ischemia.” In a comprehensive electrophysiologic study of 40 patients with chronic peripheral arterial disease (PAD), we found only minor nerve conduction changes, mainly sensory.2 In agreement with our findings, a low percentage of nerves with reduced action potential amplitudes was demonstrated in a follow-up study of patients with PAD.3

This discrepancy between the previous reports and the recent one by Weinberg et al.1 could not explain entirely the differences in the material because all three studies included patients with moderate-to-severe PAD according to the criterion of resting ankle–brachial blood pressure index (ABI). However, Weinberg et al.,1 unlike previous reports, chose patients with resting limb pain and nonhealing foot ulcers. Therefore, it is possible that, under conditions of critical limb ischemia changes of nonneural tissues (e.g., the skin, connective tissue, interstitial fluid) might pose technical limitations such as insufficient stimulation owing to high attenuation of electrical stimuli by poor volume conduction.4 Furthermore, biological abnormalities of nerve fibers, i.e., reduced nerve fiber excitability also resulting in submaximal stimulation,4 could at least partly account for the frequently observed reduction in amplitude of CMAP in the study by Weinberg et al.1 Likewise, the possibility of conduction block at the distal parts cannot be excluded, in which case measurements of F-wave latencies and persistence is far more useful than conventional maximal motor conduction. In patients with findings in the nerve conduction study, supplementary needle electromyography would be expected to confirm unequivocally axonal loss. Indeed, in our study, as well as that of England et al.,2 the major finding was the increase of duration and amplitude of motor unit potentials, indicative of chronic partial denervation. The aforementioned possible drawbacks of nerve conduction studies performed on a limb “close to amputation” reduce the importance of the reported correlation between ABI and neurophysiologic measurement.1 Such difference between patients with moderate and severe PAD was not shown in our material.2

We agree with Weinberg et al.1 that neuropathy due to PAD is uncommon in clinical practice unless a stage of critical ischemia is present. However, we believe that even in this situation abnormalities of routine nerve conduction studies should be interpreted with caution, as they may not accurately represent the neuropathic changes caused by limb ischemia.

Elisabeth Chroni, MD, PhD, Vasiliki Papapetropoulou, MD, Jiannis Tsolakis, MD, Statthis Terzis MD, Christos Psachalis, MD PhD, Theodoros Papapetropoulos, MD, Rion, Greece

Reply from the Authors: We appreciate the opportunity to clarify our conclusions regarding the effects of severe leg ischemia on peripheral nerves. We focused on the clinical features of severe (“critical”) limb ischemia but Chroni et al. raise several interesting points about the electrophysiologic data.

1. We agree that under most circumstances of mild or moderate leg ischemia, there are few significant changes in conventional nerve conduction studies. The essential difference between our patients and those of the referenced studies is in the severity of the ischemia. Our patients had either rest pain or distal skin ulcers, underscoring the severity of the distal ischemia. We would also point out that even with the lesser degree of ischemia in the patients studied by Papapetropoulou et al., there were numerous electrophysiologic abnormalities when compared with the control patients. Our interpretation is that their data supported the presence of a neuropathy.

2. A single, quite experienced electromyographer performed all of our studies. There is no reason to suspect technical error. However, we were concerned that muscle necrosis may have contributed to the reductions in CMAP amplitude. Our rationale for concluding that a neuropathy was the major or sole cause was discussed extensively in the article and based largely on the clinical syndrome and a large body of histopathologic data from human subjects that demonstrate neuropathic, not myopathic, changes in patients such as these.5,7

3. The possibility of distal conduction block was also addressed in our discussion. Rare cases of low distal CMAP amplitude from conduction block have been reported,8 but usually other demyelinating features are present. None of the CMAP in our patients showed prolonged distal latencies, temporal dispersion, or proximal conduction block.

4. We agree that needle electromyography would have been a useful addition to our study. Unfortunately, it was not part of our research protocol for gene therapy. In those patients where the data were available, motor unit remodeling consistent with reinnervation was present.

June (1 of 2) 2002 NEUROLOGY 58 1705
Cognitive deficits in patients with essential tremor

To the Editor: Lombardi et al.\(^1\) report on a series of 18 patients with essential tremor (ET) preoperatively assessed for cognition and mood and contrasted their results with similar studies in 18 patients with PD.

We retrospectively studied 55 patients with ET (34 women) for cognitive and affective state. The mean age was 57 vs 66 years in patients with PD. Lombardi et al.\(^1\) but an equal level of education to the Lombardi study at 14 ± 3 years. Our patients had milder tremor, rating scale score 12 ± 4 vs 18 ± 9. Our patients were assessed while taking no medications, whereas eight of the 18 patients in the Lombardi study were taking either propranolol or primidone; the latter is known to have potential negative cognitive effects. Results in our ET patient population were contrasted with 79 patients with cervical dystonia and tremor (CD/T). Tremor was objectively defined similarly to those with ET, utilizing an accelerometer, motus tremometer, and voice oscillographic assessments on two or more occasions with a fixed tremor rate for durations of 2 minutes or longer in each recording. In the ET population, there was a family history of tremor (49%), dystonia (2%), and scoliosis (5.5%). The last two are less frequent than in relatives of those with CD/T or CD/no T. Depression in first-degree relatives in our ET patient pool was 31% and anxiety 7%. Using Minnesota Multiphasic Personality Inventory criteria, depression occurred in 49% and anxiety in 55% of our patients with ET. Neuropsychological test performance more than 1.5 SD below age norm data was considered abnormal. Like Lombardi et al., we observed infrequent impairment of visual construction (5%) or visual memory abilities evidenced by the lower tremor ratings in our patient group vs 12 ± 4 reported by Vermilion et al.\(^2\). The minor differences in the results of the two studies should not obscure the important fact that Vermilion et al.\(^2\) have provided a replication of our results demonstrating cognitive impairment in patients with ET. Their results should provide further impetus for the study of cognitive functioning in these patients.

Drake D. Duane, MD, Kendall J. Vermilion, BS, Scottsdale, AZ

Reply from the Authors: We thank Dr. Duane and Mr. Vermilion for their comments on our article.\(^1\) We are encouraged by the results reported by Vermilion et al.,\(^2\) which demonstrate cognitive and affective impairment in a large group of patients with ET. Their results demonstrate depression, executive dysfunction, and impairment in attention, verbal learning, and verbal memory. Unfortunately, their test battery did not include a test of verbal fluency, the measure on which we obtained the largest deficits in our ET group. On those cognitive processes assessed in both studies, the data are impressively consistent. Duane and Vermilion note that on several measures, including the Digit Span\(^4\) test of auditory attention, tests of verbal learning and memory, and the Wisconsin Card Sorting Test,\(^5\) our group of patients with ET displayed greater impairment than did their patient group. Although many of our patients were taking medication for tremor control, this factor appeared unlikely to be a contributing factor in the cognitive impairment of our ET group, inasmuch as the medicated ET group outperformed the unmediated group on many of the tests in our battery. A more likely explanation for the greater severity of cognitive impairment in our patients is the greater severity of ET itself in our patients, as evidenced by the higher tremor ratings in our patient group (19.1 ± 8.2 in our study [incorrect clinical rating in Duane and Vermilion letter] vs 12 ± 4 reported by Vermilion et al.\(^2\)).

Rather than employing a cerebellar-cortical dysfunction hypothesis, we interpreted our findings to represent possible basal ganglion to cortical dysfunction. However, the difference in age, tremor duration and severity, and the use of medications in almost half of their patients makes direct comparison of these two studies difficult. In partial support of the findings of Lombardi et al.,\(^1\) however, our patients with ET were more apt to have problems in auditory verbal learning or memory than a comparison population of 79 patients with CD/T. Depression was even more prevalent in those with CD/T (72%). Furthermore, in our ET group, older patients were more prone to have cognitive performances below age expectancy than younger subjects. The differential findings between these two studies may represent stage or evolution effects in the cognitive/affective correlates of ET. We intend to expand our assessment protocol and to continue to monitor our patients over time to further assess this possibility.

Drake D. Duane, MD, Kendall J. Vermilion, BS, Scottsdale, AZ

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References


Relationship between severity of MR perfusion deficit and DWI lesion evolution

To the Editor: We were interested to read the article by Thijs et al.1 examining the relationship between severity of MR perfusion deficit and diffusion-weighted imaging (DWI) lesion evolution. We have recently published a similar analysis of sub-6-hour ischemic stroke patients with acute perfusion-weighted imaging (PWI) DWI mismatch.2 We also found that mean transit time (MTT) and cerebral blood volume (CBV) lesions closely predicted final infarct size. However, the strong correlation between acute cerebral blood flow (CBF) lesions and final infarct size in our 23 patients was not reproduced in the 12 patients studied by Thijs et al.1

Perhaps the differing methodology explains the lack of agreement. It would not be unreasonable to expect the CBF ratio to be similar to CBV ratio/MTT ratio (MTT = CBV/CBF at a pixel level). However, there are three of the 12 patients (Patients 7, 11, and 12 in the original table) in whom the CBF ratio presented exceeds the predicted CBF value by more than 25%. We wonder if reflecting the larger MTT lesion onto the CBF map led to inclusion of tissue with normal or increased CBF within the “lesion,” thus leading to a higher-than-anticipated CBF ratio.

Furthermore, as Thijs et al.1 and others have shown, the visually apparent acute MTT lesion almost always overestimates final infarct size.3,4 Therefore, patient 2 in the original table, who has a final infarct 65% greater than the acute MTT lesion, may have an artifactual result. This could be caused by the significant susceptibility artifact on the PWI maps, which the authors acknowledge.

We agree that MTT maps are the most practical of the PWI maps to use in stroke and concur that thresholded MTT maps are reasonably accurate at predicting tissue at risk of infarction. However, we believe that some caution should be applied when interpreting the CBF results of the current study, particularly in view of the small number of patients presented.

Mark W. Parsons, FRACP, P. Alan Barber, PhD, FRACP, Stephen M. Davis, MD, FRACP, Melbourne, Australia

Reply from the Authors: We appreciate the comments of Parsons et al. The focus of our study was not to predict final infarct volume using the lesion volumes identified on baseline MTT, CBV, or CBV maps, as was performed elegantly by Parsons et al.2 Our goal was to evaluate the predictive value of the relative signal intensities identified on these hemodynamic maps, rather than differentiate between the value of individual maps. Our results show that the more hyperintense the MTT lesion, the more likely the diffusion lesion was to grow to equal the size of the baseline MTT lesion. As acknowledged in the article,1 the lack of predictive value of our CBF ratios may have been caused by the small sample size, the inclusion of regions of normal or increased CBF within the “CBF lesion,” or susceptibility artifacts.

The best functional MR method to predict final infarct volume in hyperacute stroke patients is currently known. ADC, MTT, CBV and CBF, separately or in combination, have been proposed as having a high, although imperfect, predictive ability for detecting ischemic lesion growth.5-6 We suspect that discrepancies between the results of these studies are related to differences in MR acquisition technique, mathematical analysis, and definition of PWI/DWI mismatch, variable clinical inclusion criteria, and inherent biological variability. To resolve this issue, multicenter studies are needed that include large numbers of patients and uniform criteria for data acquisition and analysis. Different postprocessing methods should be directly compared to identify the method with the best predictive value. Until these important studies are performed, the superiority of one approach over another will remain unestablished.

Vincent Thijs, MD, Leuven, Belgium; Gregory W. Albers, MD, Palo Alto, CA

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References


Localization of Claude’s syndrome

To the Editor: See et al.1 revisit Claude’s syndrome, reviewing a small number of reported cases and adding six cases of their own. A recurring theme is the notion that the red nucleus is not a major site of neuropathology in the genesis of this relatively rare brainstem syndrome. This is based predominantly on MRI of their six cases and inclusion of eight previously reported cases.

I refer the authors and readers to our case study of a patient presenting with bilateral Claude’s syndrome.2 This patient presented with acute complete bilateral third nerve palsies, bilateral cerebellar ataxia, and absence of pyramidal tract signs. CT scanning was the chief diagnostic tool at the time this stroke occurred and demonstrated a hypodense midline lesion in the midbrain. On pathologic examination multiple coronal sections showed infarctions in the midline involving the inferior thalamus and the area of the subthalamic nucleus. The lesion, confirmed by microscopic examination, extended directly into the midbrain and involved the midportion of the raphe and extended into the red nucleus area on both sides.

Thus, our study does not support the minimization of the red nucleus as an important site of pathology in this syndrome. Additionally, of the eight cases not excluded from their article review of 18, two pathologically examined cases (it is unclear whether these are the only direct tissue studies, but such seems implied) also showed red nucleus involvement.

As a neurologist whose practice predates the advent of routine MRI I wish to state the obvious. The ultimate determination in correlating sites of pathology with clinical syndromes must be based on tissue examination and not solely on black and white two-dimensional images.

Additionally, neurotherapeutic intervention must first involve rational, justified, and above all, safe means. Without a stated cardiac rationale I question the initial use of IV heparin in five of the six patients.

Robert J. Coppola, DO, MS, Tampa, Florida

Reply from the Authors: We appreciate Dr. Coppola’s comments. Our findings clearly showed that lesions of the superior cerebellar peduncle just below and medial to the red nucleus is responsible for Claude’s syndrome. To our knowledge, no cases with isolated lesions confined to the red nucleus have been reported to present as Claude’s syndrome. In the case described by Coppola,1 lesions were not confined to the red nucleus or midbrain but were extended to the subthalamic nucleus, and the inferior thalamus. Cerebellar ataxia can occur because of lesions of the dentatothalamic fibers at any level from the midbrain to the thalamus. In the midbrain at the red nucleus level, a lesion may produce both ataxia and oculomotor nerve palsy. However, the lesion should be large enough to damage both oculomotor nerve fascicles and dentatothalamic fibers that run outside the red nucleus.3

We agree that imaging studies may not be the ultimate determinant in correlating the site of pathology with clinical syndromes. However, pathologic examinations are impractical in most patients with clinical syndromes of mild neurologic deficits such as Claude’s syndrome. In addition, pathologic examinations of the lesion may not be performed at the same time as a patient...
Fatigue is not associated with raised inflammatory markers in multiple sclerosis

In the letter to the editor from Dr. Jorge Iriarte (re: “Fatigue is not associated with raised inflammatory markers in multiple sclerosis,” *Neurology* 2002;58:1134–35), one of the authors was accidentally omitted. Purificación de Castro, MD, should be listed as the second author. The publisher apologizes for this error.

Ictal heart rate differentiates epileptic from non-epileptic seizures

In the article “Ictal heart rate differentiates epileptic from non-epileptic seizures” by Opherk and Hirsch (*Neurology* 2002;58: 636–638), there were some errors in the table. The authors apologize for these errors. The corrected table is printed below.

<table>
<thead>
<tr>
<th></th>
<th>Temporal lobe CPS</th>
<th>Non-epileptic staring spells</th>
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<tbody>
<tr>
<td>Ictal HR ≥130% of baseline</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>Ictal HR &lt;130% of baseline</td>
<td>6</td>
<td>28</td>
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<td></td>
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<td>29</td>
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Sensitivity: 30/36 (83%); specificity: 28/29 (97%); positive predictive value: 30/31 (97%); negative predictive value: 28/34 (82%).

CPS = complex partial seizures.
Fatigue is not associated with raised inflammatory markers in multiple sclerosis

Neurology 2002;58;1708
DOI 10.1212/WNL.58.11.1708

This information is current as of June 11, 2002