Multiple Sclerosis as an "Inside-Out" Disease

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We have read with great interest the article by Henderson and colleagues[1] in a recent issue of the *Annals*, in which the authors describe early loss of oligodendrocytes, without concomitant T-cell and B-cell infiltration or macrophage activity in tissue that borders a small selection of acute multiple sclerosis (MS) lesions. Neighboring areas with degenerate myelin were found to be infiltrated with macrophages, and fully demyelinated white matter areas contained lipid-laden macrophages, T-cells and B-cells, and immunoglobulin G deposits. These results are certainly interesting and thought-provoking. The authors' findings further strengthen the notion that MS is not so much, as has classically been argued, a primary autoimmune disease, but rather a disease starting within the central nervous system, with responses of the immune system only in later stages.

The atypical character of the cases and of the hyperacute lesions that were selected for this study may be insightful as a model for the (rapid) expansion of demyelination in the brain. However, it does remain difficult to fathom to what extent the described pathological findings are representative of the more "typical," chronic MS pathology. As reported earlier by our own group, apoptosis of oligodendrocytes in demyelinating MS lesions is rare or absent.[2] Additionally, the early loss of oligodendrocytes in nondemyelinated white matter around developing white matter lesions could not be found in our collection. A representative example of such a lesion in our material is shown in the Figure. Although an active border of major histocompatibility complex (MHC)-II–positive phagocytes can be seen in the border of the chronic active MS lesion in the Figure, as well as a clear loss of olig-2 immunopositive oligodendrocytes in the demyelinated center of the lesion, the number of oligodendrocytes in the bordering areas of normally myelinated (prephagocytosing?) white matter are similar to that of control white matter (not shown).

In addition to whether the pathological changes by Henderson and colleagues[1] can be translated to the more standard MS pathology setting, future studies should also take early degenerative changes within the axons into account. MS might be caused by a primary axonal imbalance, triggering demyelination and subsequent inflammation.[3,4] Of course, given the very intimate relation of the axon and the oligodendrocyte and its

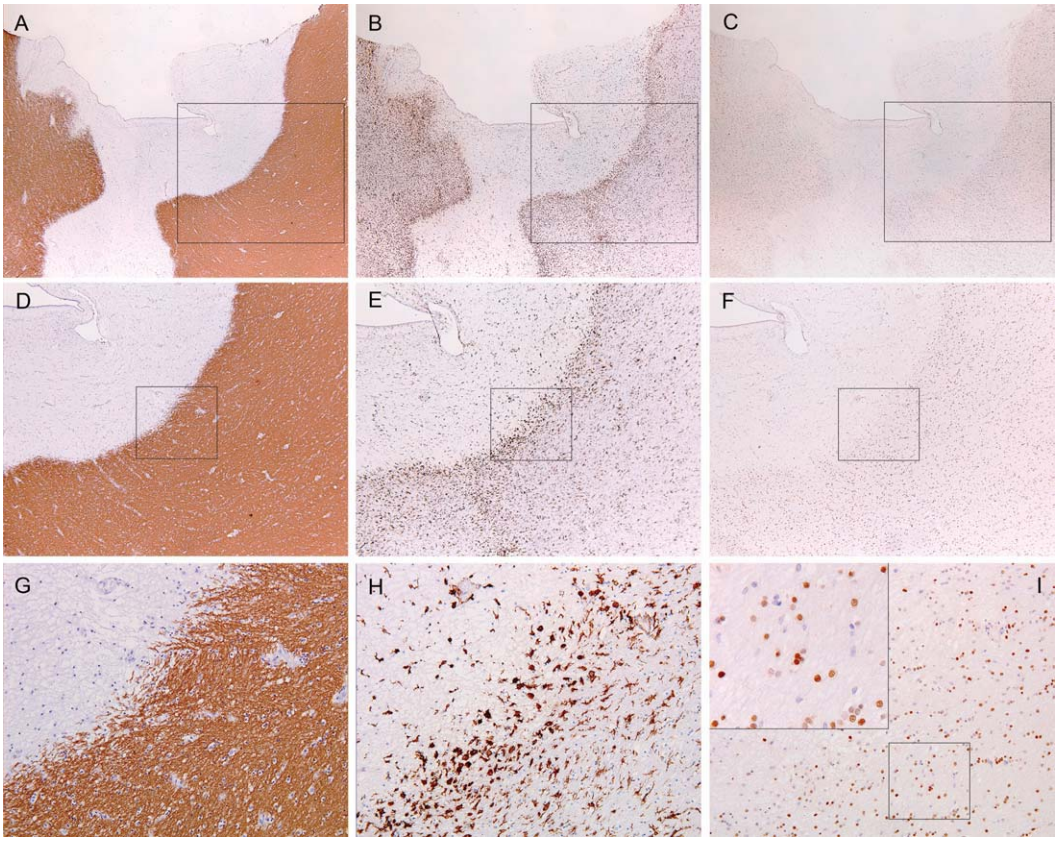

FIGURE: (A,D,G) Myelin (PLP) staining revealing a large, periventricular, chronic active MS lesion. (B,E,H) MHC-II staining showing a rim of phagocytes at the border of the same lesion. (C,F,I) Oligodendrocyte-specific transcription factor Olig-2 showing preservation of oligodendrocytes in presumed prephagocytic areas. (F,I) High-power magnifications of the border of the lesion indicating normal presence of nonapoptotic oligodendrocytes. Original magnifications: (A–C) ×12.5; (D–F) ×25; (G–I) ×100.

myelin, both the axonal hypothesis and a primary oligodendrogliopathy may be true. At the least, a balanced exploration of both ideas will further shape our concept of MS as an "inside-out" disease,[3,5] which to our opinion is a crucial issue in the currently ongoing scientific debate on what causes MS.

Potential Conflicts of Interest

Nothing to report.

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Reply

John W. Prineas, MD, Andrew P. Henderson, MD, Michael H. Barnett, MD, and John D. Parratt, MD

The "chronic active lesion" described and illustrated by Dr Geurts et al is a typical example of the most common histological type of multiple sclerosis (MS) lesion present in patients with clinically active disease of lasting several years. The authors draw attention to the fact that oligodendrocytes bordering sharp-edged, chronic demyelinated MS lesions are often normal, whereas oligodendrocytes in still-myelinated, prephagocytic, newly forming lesions as described by Henderson et al and others[1–3] are reduced in number or exhibit apoptosislike nuclear morphology. This difference, Dr Geurts et al suggest, may indicate that the mechanism of ongoing myelin destruction may not be the same in the 2 types of lesions. Although we have speculated in previous studies that myelin loss in some chronic lesions may be progressive, based on the presence of unusual microglial nodules in periplaque white matter,[4] other evidence suggests that the pathological changes exhibited by the great majority of lesions of the type described by Dr Geurts et al are those associated with arrested and not active demyelination. Oligodendrocytes and myelin sheaths in tissue immediately bordering such lesions usually appear normal in the presence of numerous activated major histocompatibility complex class 2-positive ramified microglia and lipid-containing macrophages,[4] infiltrating MRP14-positive monocytes are absent,[5] and macrophages containing particles that stain positively for myelin using Luxol fast blue or that are immunoreactive for myelin proteins are rare or absent. These chronic lesions are active, however, in the sense that robust reactive changes are present, affecting glial cells, axons, blood vessels, the extracellular matrix, and infiltrating inflammatory cells within and around the lesion.[3] These inflammatory changes are of unknown significance and have not been identified as changes that determine destruction of myelin sheaths. The only change known at present that indicates impending and inevitable destruction of myelin around an MS lesion, that is, that reliably indicates a true prephagocytic condition, is the presence of oligodendrocyte loss or apoptosis in still largely intact myelinated tissue. As noted by Dr Geurts et al and others,[4] oligodendrocytes bordering most chronic lesions usually appear normal. Why lesions with prephagocytic changes are so rarely encountered can be put down to the fact that most myelin loss and plaque expansion in MS occurs in temporally and topographically discrete increments, each preceded, we now believe, by a prephagocytic event that includes destruction of oligodendrocytes and that lasts probably no more than a few days. This also explains why such lesions have been observed only in cases of MS with unusually active and early disease.

Potential Conflicts of Interest

Nothing to report.

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Interleukin-6–174 CC Polymorphism Is Associated with Clinical Chorioamnionitis and Cerebral Palsy

Bernhard Resch, MD, PhD, and Wilhelm D. Müller, MD, PhD

We read with interest the article by Wu et al,[1] reporting on a significant association of the interleukin (IL)-6–174 CC single nucleotide polymorphism in term and near-term (≥36 weeks gestational age) infants compared to the GG type with cerebral

palsy (odds ratio [OR], 2.4; 95% confidence interval [CI], 1.3–4.4), clinical chorioamnionitis (OR, 4.6; 95% CI, 2.1–10.4), maternal age ≥35 years (OR, 2.6; 95% CI, 1.6–4.1), and male sex (OR, 1.6; 95% CI, 1.1–2.4). Based on their population data, the attributable risk percentage of the IL-6–174 CC genotype for cerebral palsy was 11.6%, which was similar to the attributable risk percentage of clinical chorioamnionitis (9.0%) and advanced maternal age (16.7%).

Cystic periventricular leukomalacia (PVL) is a leading cause of cerebral palsy in preterm infants. A recent study having found an association of the CC genotype with hemorrhagic brain injuries and white matter damage (ventriculomegaly or PVL), but not cognitive development, at 2 and 5.5 years in preterm infants ≤32 weeks of gestational age supported the speculation that infants who are genetically programmed to mount a more pronounced inflammatory response, that is, those who carry the −174 CC genotype as opposed to the GC or GG genotype, would be sicker in the perinatal period, and that this would have an impact on the prevalence of neonatal brain injury and later sequelae.[2] In a candidate gene-association study, we found no differences between mothers of children with and without PVL regarding frequencies of the IL-6–174 polymorphisms, but did find an association of the CC genotype with clinical chorioamnionitis and preterm birth, with a 3-fold increased risk for the development of PVL in the preterm offspring (OR, 3.1; 95% CI, 1.1–8.7).[3] Another finding was the association of the CC and GC genotypes with mental retardation in preterm infants with PVL.[4] Thus, as shown by data from Wu and colleagues[5] demonstrating that chorioamnionitis is an independent risk factor for cerebral palsy even among term and near-term infants, the C allele seems to modify the severity of perinatal brain injury via an exaggerated fetal inflammatory response syndrome.

Potential Conflicts of Interest

Nothing to report.

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Reply

Yvonne W. Wu, MD, MPH[1] and Lisa A. Croen, PhD[2]

We thank Drs Resch and Muller for their helpful comments. We agree that the fetal inflammatory response syndrome appears to play a role in mediating perinatal brain injury and cerebral palsy (CP), and that genetic association studies may shed further light on this matter. We are also aware of the caution needed in interpreting the results of candidate gene association studies.[1] This is especially true for the interleukin (IL)-6-174 polymorphism, given the conflicting results of previous studies. Although some newborn studies, including ours, have linked the less common C allele with increased IL-6 production and with adverse neonatal outcomes, other studies have reported the opposite finding; for example, the C allele appears to confer decreased risk of maternal chorioamnionitis in the mother.[2,3] It is crucial to replicate genetic association study findings in other populations. Therefore, we read with great interest a recent Australian study that reported a 10-fold increased risk of spastic quadriplegic CP in infants with the C allele at the IL-6-174 polymorphism,[4] which corroborates our finding.[5] Furthermore, Drs Resch and Muller point to their interesting study of maternal IL-6-174 polymorphism and periventricular leukomalacia (PVL), a strong risk factor for CP.[6] They found that mothers of infants with PVL who experienced chorioamnionitis were 3× more likely to have the CC genotype than control mothers of unaffected infants. It would be helpful to further determine whether the CC genotype is more common in mothers of infants with PVL who experienced chorioamnionitis, when compared to control mothers who also experienced chorioamnionitis, because this would provide even stronger evidence for the IL-6 C allele as a causal factor in the pathogenesis of PVL. As a note of clarification, the letter from Drs Resch and Muller lists several odds ratios (OR) for CP from our study (eg, for clinical chorioamnionitis, advanced maternal age, and male sex).[5] These ORs refer to the degree of elevated risk of CP associated with each factor, and have nothing to do with the IL-6 polymorphism as implied by the letter. Additional studies of IL-6 genetic variation and the neonatal inflammatory response syndrome will further illuminate the role of inflammation in perinatal brain injury.

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Potential Conflicts of Interest

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The Challenge of Causal Inference

Olaf Dammann, DrMed, SM,[1] and Alan Leviton, MD, SM[2]

Two recent articles in *Annals of Neurology* addressed the issue of causal inference from epidemiologic data. One discussed the "difficulty of going from association to causation in human epidemiology" in the context of virus exposure and multiple sclerosis.[1] The other summarized the editors' perception that a study on abdominal obesity and brain volume published in the Journal[2] "does not tell us that abdominal obesity causes brain atrophy; it only describes an association between the 2 characteristics."[3]

Statements on causal inference from observational data prevail in the medical literature despite the recognition that "causation cannot be seen. Causation cannot be proven … Nor can causation be made certain. It is, at best, an expert's judgment, at worst, an expert's guess."[4] Unfortunately, even the current litmus test in clinical epidemiology, the randomized controlled trial, might be less reliable than most would like it to be, because even controlled trials match only on a few characteristics of the individuals randomized, leaving much room for both measurable and unmeasured (residual) confounding.

Alas, the ongoing debates in philosophy[5] and epidemiology[6] suggest that we are probably waiting for Godot when expecting within our lifetime a simple, definitive answer to the questions, "How do we define a 'cause' in the health sciences, and how do we know it when we see it?" We propose that the notion of "causes" be dropped in favor of a notion of "contributory factors," revealed only by taking a holistic look at many studies (wet lab, clinical epidemiology, public health intervention) at multiple levels (genetic, molecular, cellular, tissue, individual, population) that will help identify worthwhile targets for interventions that will, in turn, improve human health.[7] In essence, we suggest that the answer will come after completion of an integrated research program that includes basic experimental, human observational, and human intervention studies.[8] But even then, it is still possible that all these studies will attribute causal powers to characteristics that are actually due to bias or chance.

This brings us back full circle to the uncertainty claim above. Is the identification of causation in biomedicine ultimately elusive? Some who study and teach philosophy for a living suggest that the causal relation "is the set of causal beliefs that an agent with total evidence should adopt" (emphasis in original).[9] Stay tuned.

Potential Conflicts of Interest

Nothing to report.

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Visceral Obesity and Brain Volume

Adam E. Handel, BA, BMBCh,[1,2] Giulio Disanto, MD,[1,2] and Sreeram V. Ramagopalan, MA, DPhil[1,2]

We read with interest the recently published article revealing a strong relationship between visceral obesity and brain volume.[1] Avoiding obesity appears to be important not only for general health but for preserving cognitive capacity later in life. The authors suggest a number of potential mechanisms as to how visceral fat may affect brain volume, but we feel that there is 1 potential factor that was not discussed, namely altered metabolism as a result of obesity. The importance of micronutrients and vitamins for optimal health is well known. One in

particular that is proving to be of increasing importance is vitamin D.[2] Vitamin D_3 is fat soluble. Therefore, in obese individuals, fat can sequestrate vitamin D, making it unavailable for use, further increasing the risk of vitamin D deficiency, which is highly prevalent in the United States.[2] Indeed, serum levels of vitamin D correlate inversely with body mass index (BMI), and obese individuals require much higher levels of vitamin D supplementation to reach a sufficient serum level of vitamin D.[2,3] Vitamin D deficiency is involved in a plethora of physiological processes, including neuronal function and the immune response.[2,4] Vitamin D-deficient rats show alterations in brain development and behavioral measures in adulthood.[4] It is thus possible that it is actually vitamin D deficiency that underlies the association of visceral obesity with brain volume. It would therefore be of interest to measure vitamin D levels in the patients studied by Debette and colleagues.[1] Although we have highlighted vitamin D, this altered metabolism as a result of obesity is also true for other micronutrients. If vitamin D or other micronutrient deficiency is responsible for the observed reduction in brain volume in obese individuals, supplementation may be important as a preventative public health measure.[2] Furthermore, advice on recommended daily amounts of micronutrients may need to be changed to incorporate a range of daily intake values for the complete spectrum of BMI. This also applies more generally to other factors, including treatments.[5] Nutritional status and metabolism should be further studied in obese individuals so that simple steps to avoid a potentially growing burden of cognitive decline can be taken.

TABLE 1. Association of Obesity Indices with Total Brain Volume without and with Adjustment for Baseline Circulating Vitamin D Levels

	n	TCBV (beta ± SE)	*p*
Body mass index			
All: Model 1	728	−0.35 ± 0.11[a]	0.002[a]
Subset with vitamin D levels			
Model 1	422	−0.26 ± 0.14	0.065
Model 2	422	−0.24 ± 0.14	0.092
Waist circumference			
All: Model 1	725	−0.41 ± 0.11[a]	0.003[a]
Subset with vitamin D levels			
Model 1	423	−0.27 ± 0.14	0.060
Model 2	423	−0.25 ± 0.15	0.087
Waist-to-hip ratio			
All: Model 1	723	−0.48 ± 0.12[a]	<0.001[a]
Subset with vitamin D levels			
Model 1	423	−0.33 ± 0.15[a]	0.030[a]
Model 2	423	−0.32 ± 0.15[a]	0.035[a]
Subcutaneous adipose tissue			
All: Model 1	733	−0.29 ± 0.11[a]	0.011[a]
Subset with Vitamin D levels			
Model 1	423	−0.18 ± 0.14	0.215
Model 2	423	−0.16 ± 0.15	0.282
Visceral adipose tissue			
All: Model 1	733	−0.44 ± 0.11[a]	<0.001[a]
Subset with vitamin D levels			
Model 1	423	−0.40 ± 0.15[a]	0.008[a]
Model 2	423	−0.38 ± 0.15[a]	0.013[a]

[a]Significant.
Beta = effect estimate; Model 1 = adjusted for age, sex, and time interval between abdominal computed tomography and brain MRI; Model 2 = additionally adjusted for vitamin D levels; SE = standard error of beta; TCBV = total brain volume.

Potential Conflicts of Interest

Nothing to report.

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Reply

Stéphanie Debette, MD, PhD,[1,2] Alexa Beiser, PhD,[1,2,3] Thomas J. Wang, MD,[1,4] Charles DeCarli, MD,[1,5] Philip A. Wolf, MD,[1,2] Caroline S. Fox, MD, MP,[1,6,7] and Sudha Seshadri, MD[1,2]

We thank Dr. Handel and colleagues for their interesting commentary suggesting that the inverse association we observed between visceral adiposity and total brain volume might be mediated by metabolic factors, specifically changes in vitamin D levels. Indeed, vitamin D levels are inversely associated with body mass index, subcutaneous adiposity, and visceral adiposity in the Framingham Offspring.[1]

Vitamin D levels were available at the baseline examination in a subsample of 423 participants (53% women; mean age: 59 ± 9 years) among the 733 included in our study.[2] Mean vitamin D level in this subsample was 20 ± 7 ng/ml. We, like others,[3] did not observe an association of vitamin D with total brain volume (TCBV) in our subsample. We nevertheless looked for a potential confounding effect of vitamin D levels on the inverse association between adiposity measures and TCBV. We first ran our main regression model in the subset of 423 participants with vitamin D levels available (Table 1). Despite the reduced sample size we still observed an inverse association of waist-to-hip ratio and visceral adipose tissue volume with TCBV. These associations remained significant after additionally adjusting for vitamin D levels (see Table 1).

Thus, in the present sample we do not find that Vitamin D is an important mediator in the inverse association of visceral adiposity with TCBV. This does not exclude a possible mediating role of vitamin D for the association of visceral adiposity with cognitive decline and dementia.[4]

Potential Conflicts of Interest

Nothing to report.

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