No Cytomegalovirus DNA in Sera from Patients with Anti-MAG/SGPG Antibody–Associated Neuropathy

Sachiko Irie, MD, PhD,* Naomi Kanazawa, BS,† Mieko Ogino, MD, PhD,* Toyokazu Saito, MD, PhD,* and Tadao Funato, PhD‡

In a recent study by Yuki and colleagues, cytopneumatovirus (CMV) DNA was detected in sera from 23 of 26 patients (88%) with IgM anti–myelin–associated glycoprotein (anti-MAG)/sulfated glucuronyl paragloboside (SGPG) antibody–associated neuropathy. Anti-MAG/SGPG antibody–associated neuropathy is a slowly progressive neuropathy and generally occurs in elderly patients with IgM M proteinemia. It has been experimentally confirmed that immunization with MAG and transfer of anti-MAG/SGPG antibodies cause demyelinating neuropathy. Yuki and colleagues suggested that CMV infections induce IgM anti-MAG/SGPG antibodies based on the results of their study.

We also examined serum CMV DNA by means of the polymerase chain reaction (PCR) assay in 13 patients with IgM M proteinemia and anti-MAG/SGPG antibody–associated neuropathy. Serum IgM anti-MAG antibodies were detected by immunoblotting, and serum IgM anti-SGPG antibodies were detected by thin-layer chromatography immunostaining. For the PCR, primers were synthesized from genomic CMV DNA sequences based on the major immediate early gene of the Towne strain, which were confirmed not to cross-react with other herpes viruses. The PCR was also performed in all of these patients using primers derived from the early gene corresponding to the DNA polymerase of CMV. In the PCR for both genes, serum CMV DNA was negative in all patients, in 1 of whom it was examined at another point during the course of the study. CMV DNA was also negative in blood cells from 3 patients.

CMV usually causes latent infections throughout life. Ninety-five percent of the Japanese population has latent CMV infections. In compromised hosts, including fetuses, transplant patients, and acquired immunodeficiency syndrome patients, CMV causes pantropic organic disturbances. A CMV infection is confirmed by the detection of CMV DNA in samples of organs or tissues obtained by biopsy. CMV DNA detection in serum or blood cells should indicate the activation or reactivation of CMV. Therefore, primary infections or reinfections could occur in patients with CMV DNAemia. Yuki and co-workers did not mention whether their patients showed symptoms caused by direct CMV infections or whether they had high titers of serum IgG anti-CMV antibodies representing continuous CMV infections.

In conclusion, we could not find any correlation between anti-MAG/SGPG antibody–associated neuropathy and serum CMV DNA. Further investigations are necessary to clarify whether patients with anti-MAG/SGPG antibody–associated neuropathy have CMV DNAemia or not.

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References


Reply

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A positive correlation between the detection of infectious cytopneumatovirus (CMV) in leukocytes and CMV DNA in serum and plasma has been reported. The polymerase chain reaction (PCR) detected CMV DNA in serum and plasma from patients with primary CMV infection as well as reactivated CMV infection. The PCR-amplified CMV DNA was detected in serum and plasma only when active CMV infection was suspected, suggesting the presence of extracellular free virus in serum and plasma during the active CMV infection. Irrespective of the status of the serology results, no CMV DNA was amplified in serum and plasma from healthy subjects.

The DNA extraction procedure may be critical for ensuring the sensitivity of the PCR. Hamprecht and co-workers have reported that PCR assay from proteinase-K supernatants is less sensitive than PCR assay from phenol/chloroform extracts of serum and plasma. A method of proteinase-K digestion followed by heating and centrifugation prior to amplification did not enhance or even decreased the detection limits compared with amplification of the native material. The standard extraction procedure of phenol/chloroform extraction followed by ethanol precipitation is the most sensitive detector of DNA from serum and plasma. Serum is more suitable than plasma for the detection of low copy numbers of CMV DNA, however. In addition, Kimura and colleagues have reported that heparin inhibits the PCR amplification and could not be removed from the plasma using the standard DNA extraction method and that the yield of amplified products decreases approximately 1- to 100-fold. Our glass powder method for extracting DNA from serum and plasma is highly efficient at eliminating the PCR inhibitors, however. PCR using DNA treated with glass powder is more sensitive than PCR using DNA extracted by phenol/chloroform. In our system, CMV DNA could be detected at levels of 100 copies per cell by ethidium bromide–stained gel after PCR amplification, and Southern blot hybridization revealed 1 copy per cell. We observed a high frequency of detection of CMV DNA in sera from patients with IgM anti-MAG/SGPG antibody–associated neuropathy. CMV DNA was detected in 4 of 23 PCR-positive patients using ethidium bromide–stained gels and in 19 patients by hybridization. These results indicate that 1 to 100 copies of CMV DNA were present in 1 μl of serum from most of the patients with anti-MAG/SGPG antibody–associated neuropathy.
Irie and his associates performed a PCR assay according to the method of Funato and colleagues (written in Japanese with an English abstract). This real-time PCR method is a rapid and accurate assay for the detection and quantitation of viral DNA and can detect 10 to over $10^7$ copies of DNA with a wide linear range. PCR in serum and plasma is much less sensitive than that in leukocytes in the quantitative determination system, however. No DNA was detected in plasma from some patients in the system of Funato and colleagues, although a high copy number of CMV DNA was observed in blood from the patients. Patients with IgM anti-MAG/SGPG antibody often receive plasma exchange, and plasma samples are stored in laboratories. We recommend that Irie and his colleagues check to determine whether they used such plasma for their investigation. Furthermore, they did not mention the method of DNA extraction. It is possible that the inhibitor was not removed from the sample and that the sensitivity of the PCR was thus decreased. In such case, it might be that no amplification was observed in serum.

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**References**


**The Pocket Monsters Episode**

G. F. A. Harding, DSc, PhD, BSc, Hon MRCP, FBPsS, CPsychol

I was interested to read the article of Tobimatsu and colleagues in *Annals of Neurology*. Their findings completely replicate my own findings in relation to the *Pocket Monsters* incident of December 16, 1997.

They do not, however, in their discussion, reference my description of chromatic sensitivity contained in that paper, which is identical to their suggested mechanism with one exception. They do not indicate that the television red gun of the cathode ray tube is capable of producing only long wavelength red. For this reason, when I proposed the Japanese television guidelines for both NHK and the Commercial Broadcasters Association of Japan, the use of the red gun of the television at a rate greater than 3/sec was condemned. The British guidelines, which had been in existence for a number of years, were similarly modified.

Certainly, from our present experiments, long wavelength red interspersed with blue frames is more provocative than equilumintant green frames. This does not indicate that red per se, rather than long wavelength red, will also be equally provocative, since a red matched to the sensitivity of human cones is certainly not more provocative than other colors. It may be, therefore, that chromatic sensitivity is dependent on the overlap of the human cone wavelength sensitivity and the relative excitation of the cones, and that if any cone system is stimulated in isolation it may be equally provocative.

From a practical viewpoint, the value of television guidelines is clearly indicated. Although NTSC television systems, with their 60-Hz refresh rate, are inherently more safe than PAL systems (15% patient sensitivity versus 49% sensitivity), if the wrong material is transmitted, the risk is as great. In addition, PAL systems inherently precipitate more patients annually, so that in countries using NTSC there is an unknown pool of photosensitive individuals who will become patients when provocative material is transmitted.

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**References**


**Reply**

Shozo Tobimatsu, MD,* You Min Zhang, MD,* Yasuko Tomoda, MD,† Akihisa Mitsudome, MD,† and Motohiro Kato, MD*

We thank Dr Harding for his particular attention to our report. He raises several important issues that should be clarified.

We agree that chromatic sensitivity depends on the overlap of the human cone wavelength sensitivity and the relative excitation of the cones. Dr Harding, however, considers that
the red frame (long wavelength red) only stimulates the red cones and that no antagonistic effects are elicited from the other cone populations, thus resulting in a maximal stimulation of the visual cortex.¹ It has been shown that if red or green cones are stimulated in isolation, it is equally provocative in photosensitive epilepsy (PSE).² Both our findings and his also revealed that rapid blue-red color changes are more provocative than monochromatic ones. It is well known that no antagonistic relationship exists between the red and blue cone impulses but not between the red and green cone impulses in the visual cortical neurons.³ Therefore, we pointed out the possibility that no matching inhibitory signals are elicited by stimulation with a combination of red and blue. This results in the maximal stimulation of the visual cortex and seizures in photosensitive individuals. Furthermore, we also proved the high provocation of red and blue stimulation in terms of stimulus frequency: we found that blue-red stimuli provoked a photoparoxysmal response (PPR) even at a lower stimulus frequency when compared with achromatic ones. We discussed the physiological nature of the high-risk PPR on the basis of photosensitivity, pattern sensitivity, chromatic sensitivity, and stimulus frequency, and concluded that our patients had “chromatic sensitivity,” a term Dr Harding did not use specifically.

The subjects of our study included 4 patients who suffered epileptic seizures while watching a popular animated TV program, Pocket Monsters, without any previous history of afebrile convulsions. This is different from Dr Harding’s study, in which he tested 6 patients with PSE who had minimal photosensitivity or who had been receiving valproic acid. Since 2 of the 4 children in our study did not show a PPR in response to intermittent photic stimulation in the routine electroencephalographic examination, our patients seem to have had a much lower risk for photosensitivity than his patients. These results led us to propose a new subcategory of PSE called “chromatic sensitive epilepsy,” which thus demonstrates that our study did not simply duplicate his study.

Finally, we consider that this episode may be the world’s largest simultaneous occurrence of photosensitive symptoms in children provoked by viewing a television program. Apparently, the seizures were considered to be triggered by a single uniform visual stimulus: rapid color changes between blue and red in the cartoon. Hence, our patients watched the cartoon via the regular domestic TV system in Japan with a frame rate of 60 Hz; they were therefore at a lower risk than for a TV system with a frame rate of 50 Hz.¹ We therefore agree with Dr Harding’s opinion that television guidelines are necessary to prevent such seizures in the future.

References

Seasonal Fluctuations of Gadolinium-Enhancing Magnetic Resonance Imaging Lesions in Multiple Sclerosis

Dorothee Auer, MD,* Erina M. Schumann, MD,* Tania Kumpfel, MD,† Christoff Gössl, MSc,* and Claudia Trenkwalder, MD†

Serial magnetic resonance imaging (MRI) has been propagated for pilot studies on therapeutic efficacy in multiple sclerosis (MS), because gadolinium (Gd)-enhancing lesions reflect disease activity at least five times more sensitively than clinical assessment.¹² Power calculations from MRI data in the natural course of the disease proved that a crossover design with monthly MRI scans for 6 months before and after therapy is most effective in terms of the required sample size.¹ However, seasonal fluctuations in the frequency of Gd-enhancing lesions, which may be expected from known variations in clinical bouts,³⁴ may confound such a design and were addressed in this retrospective study.

A total of 202 MRI examinations, performed between May 1996 and May 1999 in 53 patients with relapsing–remitting (RR) or secondary progressive (SP) MS, were included; 27 patients were followed, with monthly MRI scans as part of the run-in period of a treatment trial, and 26 mostly inpatients were referred for clinical exacerbations. All patients were untreated at the time of the MRI scan and had not received immunosuppressant therapy for at least 8 weeks before the examination. The monthly rate of active studies (percentage of the total number of studies [n actles] and the average number of enhancing lesions per month [n actles]) were calculated.

There was a clear biphasic seasonal fluctuation (Fig) of the disease activity, which was highest in spring and early summer (n actles, 4.1 in April) and lowest in autumn (n actles, 0.77 in October). The n actles was significantly higher in the first compared with the second half of the year (p < 0.006, analysis of variance).

This study, for the first time, demonstrates an annual rhythm of enhancing MRI lesions in RR-MS and SP-MS patients, indicating seasonal fluctuations in subclinical disease activity. The pattern in this south German population closely resembles the course of the frequency of onsets and exacerbations in RR-MS in Switzerland and Arizona.¹ Sea-sonal variations in viral infection rates may partly explain the effect, because viral infections are more common in spring and have been shown to increase the relative risk for a relapse. However, fewer than one-third of all relapses coincide with infections; moreover, a recent study failed to demonstrate a definite relation between enhancing MRI lesions and at-risk periods defined by symptomatic or serologically confirmed upper respiratory tract infections.⁵ It is conceivable that climatic factors, such as temperature, amount of sunlight, and ultraviolet light exposure, may also be involved.

First evidence of a seasonal change in immunoregulation was recently provided in progressive MS; that is, production
of interferon, a cytokine involved in the early pathophysiological events of clinical attacks, has been found to be upregulated in autumn and winter. It is noteworthy that the peak occurred in autumn in this group of patients from New England, in contrast to the nadir of MRI activity we observed in October. Similar geographical differences have been noted in the seasonal peaks of clinical attacks.

In view of MRI-based exploratory therapeutic trials, the marked seasonal variation of Gd-enhancing lesions in MS patients may (dis-)simulate treatment effects. Appropriate modification of crossover designs and the statistical model will further enhance usefulness of MRI to detect treatment effects. In addition, the presented findings indicate high-risk and low-risk periods for subclinical disease activity. Systematic review of Gd-enhanced MRI scans of MS populations may thus offer a basis for possible tailoring of prophylactic treatment regimens.

References

Intracellular Adhesion Molecule-1 Polymorphisms and Genetic Susceptibility to Multiple Sclerosis: Additional Data and Meta-Analysis
Joep Killestein, MD,* Hans M. Schrijver, MD,* J. Bart A. Crusius, BSc,** Carmen Pérez, Biol,†† Bernard M. J. Uitdehaag, MD, PhD,* A. Salvador Peña, MD, FRCP,**‡ and Chris H. Polman, MD, PhD*

Two recent studies have addressed gene polymorphisms in the intercellular adhesion molecule-1 (ICAM-1) gene as potential determinants of susceptibility for multiple sclerosis (MS). Two amino acid polymorphisms have been investigated: Gly (G 241) or Arg (R 241) at codon 241 in exon 4 and Lys (K 469) or Glu (E 469) at codon 469 in exon 6.1

In the first study, Mycko and associates2 reported that the allele distribution of the ICAM-1 K 469 allele was significantly increased in Polish MS patients, reflecting a 21% higher frequency of the KK genotype and a 19% lower frequency of the EE genotype compared with controls (Table). The allele distribution and genotype frequencies of the ICAM-1 G/R 241 polymorphism were not significantly different in MS patients compared with controls. In a recent letter by Luomala and colleagues,3 the suggestion that the KK genotype might be associated with MS and the EE genotype might be protective was not confirmed for the Finnish population (see Table). However, the Finnish study showed that the frequency of the heterozygous EK genotype was 15% lower in patients than in controls.

We genotyped 145 unrelated Dutch caucasian MS patients (34 relapsing-remitting, 74 secondary progressive, and 37 primary progressive) and 106 unrelated ethnically matched healthy controls. In this study, the largest of the three, the allele distribution and genotype frequencies of ICAM-1 polymorphisms in exons 4 and 6 were not significantly different for MS patients compared with controls and were not significantly different between MS subgroups as well. If any, the trend for the genotype K/E 469 polymorphism was in the opposite direction of that in the Polish and
the Finnish study (see Table). The frequency of the KK genotype was 9% lower in patients with MS than in controls, thereby disqualifying it as a susceptibility marker in MS. The frequency of the heterozygous EK genotype was 7% higher in MS patients compared with controls, not supporting the presence of a protective effect.

Performing a meta-analysis by the Mantel-Haenszel method and bringing together the findings of all three studies (315 European MS patients and 287 controls), no significant differences in allele and genotype frequencies between MS patients and controls could be sustained (see Table). Based on these observations, we conclude that there is no firm evidence for the involvement of the ICAM-1 gene exon 6 polymorphism in MS susceptibility.

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This work was supported by a grant from Serono Benelux BV.

## References


## Reply

Mari Luomala, MSc,* Irina Elovaara, MD, PhD,† Timo Koivula, MD, PhD,* and Terho Lehtimäki, MD, PhD*‡

The study of Killestein and colleagues found no association of the intercellular adhesion molecule-1 (ICAM-1) gene exon 6 polymorphism with multiple sclerosis (MS) in the Dutch population. In contrast, our preliminary study from Finnish population suggested that EK genotype of ICAM-1 is a protective marker,¹ whereas the study from the Polish population found the KK genotype as a susceptible marker in MS.² The heterogeneity of the disease in relation to geographical stratification and ethnicity of population may be factors explaining different results in these three studies. For example, our study was focused on the genetically isolated Finnish population. Thus, it may be difficult to compare the results from different populations. Also, gender and clinical subtype of the disease could be confounding factors to be considered.

We have now extended our initial study by investigating 104 unrelated Finnish patients with MS and 111 sex- and age-matched healthy Finnish subjects. The data were also analyzed in relation to gender and the clinical subtype of MS. We found a trend suggesting negative association between the EK genotype and a positive association between the KK genotype and MS (Table on page 279). The frequencies of the KK genotype and K allele were significantly increased in female patients with secondary progressive MS (11/23 vs 14/68, p = 0.01, and 33/46 vs 64/136, p = 0.004, respectively) and chronic progressive forms of MS (secondary progressive and primary progressive MS analyzed together: 16/37 vs 14/68, p = 0.01, and 50/74 vs 64/136, p = 0.004, respectively) when compared with female controls (see Table).

It is obvious that the genetic heterogeneity of MS may be reduced by analyzing different subsets of patients, although these kinds of analyses are a problem statistically. It is interesting that the genotype associated with MS in the Polish study² was linked to the specific subset of female patients in

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### Table. The Frequencies of ICAM-1 Exon 6 Polymorphism in Multiple Sclerosis (MS) Patients and Controls

<table>
<thead>
<tr>
<th>Studies</th>
<th>Allele (%)</th>
<th>Genotype (%)</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>E</td>
</tr>
<tr>
<td>Dutch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MS patients</td>
<td>145</td>
<td>48</td>
</tr>
<tr>
<td>Controls</td>
<td>106</td>
<td>42</td>
</tr>
<tr>
<td>Polish</td>
<td></td>
<td></td>
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<tr>
<td>MS patients</td>
<td>79</td>
<td>32</td>
</tr>
<tr>
<td>Controls</td>
<td>68</td>
<td>51</td>
</tr>
<tr>
<td>Finnish</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MS patients</td>
<td>91</td>
<td>48</td>
</tr>
<tr>
<td>Controls</td>
<td>113</td>
<td>47</td>
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<tr>
<td>Total</td>
<td></td>
<td>315</td>
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<tr>
<td></td>
<td></td>
<td>287</td>
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</tbody>
</table>
Table. Frequencies of Intercellular Adhesion Molecule-1 Exon 6 Polymorphism in Controls and Multiple Sclerosis (MS) Patients

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Allele</th>
<th>Genotype</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>E</td>
<td>K</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Controls</td>
<td>111</td>
<td>109 (49)</td>
</tr>
<tr>
<td>Female controls</td>
<td>68</td>
<td>72 (53)</td>
</tr>
<tr>
<td>MS total</td>
<td>104</td>
<td>95 (46)</td>
</tr>
<tr>
<td>Females with MS</td>
<td>59</td>
<td>47 (40)</td>
</tr>
<tr>
<td>Females with RRMS</td>
<td>22</td>
<td>20 (49)</td>
</tr>
<tr>
<td>Females with SPMS</td>
<td>23</td>
<td>13 (28)</td>
</tr>
<tr>
<td>Females with PPMS</td>
<td>14</td>
<td>11 (39)</td>
</tr>
</tbody>
</table>

RRMS = relapsing-remitting MS; SPMS = secondary progressive MS; PPMS = primary progressive MS.

Differences in allele distributions were (by $\chi^2$ test) as follows: $^a$ females with MS vs female controls, $p = 0.04$; $^b$ females with SPMS vs female controls, $p = 0.01$; $^c$ females with RRMS vs female controls, $p = 0.004$; $^d$ females with SPMS or PPMS vs female controls, $p = 0.004$.

Differences between KK vs EE and EK genotypes were (by $\chi^2$ test) as follows: $^e$ females with MS vs female controls, $p = 0.04$; $^f$ females with SPMS vs female controls, $p = 0.01$; $^g$ females with SPMS or PPMS vs female controls, $p = 0.01$.

References


Subtle Brain Abnormalities in Children with Sickle Cell Disease: Relationship to Blood Hematocrit
Juan P. Rivera, MD

I read with interest the article by Steen and colleagues$^1$ and was indeed surprised at the significant abnormalities seen in the full-scale intelligence quotient (FSIQ) scores. However, as I looked a little closer at the data I was concerned about the validity of the results based on the following. The study included 1 subject that had the lowest hematocrit combined with the lowest FSIQ score; both of these values were far below the 2 standard deviations seen even in a $t$ distribution. The study size itself resulted in a total of 19 patients with both hematocrit and FSIQ data available. The significance of this variation from normality should not be dismissed. For example, if the patient truly had a hematocrit of 7.5, the hemoglobin concentration would be at best 3 to 4 mg/dl and the arterial oxygen delivery of this patient’s blood without using continuous oxygen would calculate out to be less than 50% of normal (not including the effect of hemoglobin (Hb) SS on the oxyhemoglobin dissociation curve). This patient as expected would have a brain attempting to function in the hypoxic range, and as stated by the authors the patient would theoretically be in sickle cell crisis during the testing. As such, the question then becomes, is a study of 19 patients in which 1 patient falls far below the expected normality, thus shifting the possible means much lower than expected (which is what the authors report) truly valid.

Additionally, the authors comment on the findings that the result of the lower FSIQ scores could not be explained by absence from school or educational deficits because of the lower scores being found in the younger patients. However, they made no mention of regression of FSIQ based on age or hematocrit based on age. It is therefore possible that the younger patients scored lower on FSIQ as a result of the greater impact Hb SS has on the younger population and the older patients who were likely to have not been affected by Hb SS as frequently as the younger population. They may have in fact had the opportunity to recover from the effects of missing education during the early years of schooling. This would actually be supported if the authors’ statement that the younger patients had the lowest FSIQ scores as stated earlier the prevalence of changes in MRI “silent infarctions” are not seen after age 6.

I would like to see the study performed on a larger population of patients. I think the results would be very intriguing from a socioeducational standpoint, as it would then identify a group of people at risk and potentially entitle them to legislative guarantees to more specialized education.

Reference

Reply
R. Grant Steen, PhD,*†§ Xioping Xiong, PhD,1 Raymond K. Mulhern, PhD,§ James W. Langston, MD,*† and Winfred C. Wang, MD§#

Dr Rivera raises an excellent point in his letter about our article by Steen. Analysis that relies on correlation is prone to error if there are outliers in the data. However, we believe that the correlation we report, a direct relationship between full-scale intelligence quotient (FSIQ) and hematocrit in children with sickle cell disease, is not an artifactual finding.

The relation between hematocrit and FSIQ does not change significantly if the patient with the lowest hematocrit is excluded from analysis. When Figure 2 from the paper is replotted, after deleting the patient in question, the results are unchanged (Fig). With the lowest-hematocrit patient included, the correlation coefficient is $r = 0.764$; without this patient, $r = 0.695$. Both values are highly significant ($p < 0.001$ and $p = 0.014$, respectively). In fact, close inspection of the original figure shows that there is a clear trend to the data without this patient.

As stated in the article, we believe our results “cannot be explained by disease-related school absence or inadequate educational access” because “none of the psychometric measures was significantly correlated with age; because cognitive deficits were present in the youngest children we examined, and because such deficits did not worsen with age.” What was not stated in the article is that age and hematocrit are also not correlated. Therefore, we believe we cannot attribute cognitive deficit to anything other than the disease process itself.

There is no evidence to date to support a hypothesis that older patients can compensate for lost educational time as they age. In fact, this is the opposite of what seems to be emerging from the CSSCD data. Patients tend to fall further and further behind academically, probably as a result of ongoing insult to the brain and cumulative loss of academic training.

We agree with Dr Rivera that these children should be entitled to every bit of help possible. This is a devastating disease. We have begun an NIH-funded prospective longitudinal study of patients and their siblings in which we plan to enroll subjects aged 4 to 7 years and to follow them for 4 years. We anticipate that this study will provide a rationale for more aggressive intervention in the disease process.

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*Fig. Revision of original Figure 2. Regression of full-scale intelligence quotient (IQ) against patient blood hematocrit (%), measured within several months of psychometric testing. Data have been replotted, excluding the patient with the lowest hematocrit.