Dementia is a major predictor of death among the Italian elderly

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Cerebellar degeneration associated with HIV infection

To the Editor: HIV type 1 (HIV-1) infection can produce neurologic complications such as dementia, myelopathy, and peripheral neuropathy. Tagliati et al.[1] described 10 such patients with symptoms of cerebellar dysfunction that they similarly ascribed to HIV-1 infection. These patients were screened for toxic and neoplastic etiologies of cerebellar degeneration. However, no genetic testing was performed. This sample was quite heterogeneous. Although ataxia was present in all 10 patients, and dysmetria in 9, other cerebellar symptoms including tremor (4 patients), nystagmus (3 patients), and dysdiadochokinesis (6 patients) were less prevalent. Radiologic imaging showed severe cerebellar atrophy in 4 patients, and mild-moderate atrophy in 3 others. Imaging was not performed on 3 patients. Pathologic studies demonstrated cerebellar granular cell loss in only 2 out of 3 autopsied patients. Do such variegated data truly define an HIV-1 related cerebellar disorder? The following report demonstrates that HIV-1–infected individuals may have superimposed genetic disorders that need to be excluded before concluding such a syndrome exists.

A 33-year-old man presented in October 1998 with a 1-year history of progressive gait ataxia, dysarthria, and clumsiness. HIV-1 infection had been diagnosed in 1985. He denied any history of alcohol or drug use or opportunistic infections. His viral load was undetectable (less than 50 copies per milliliter) and his CD4 count was 733 cells per mm^3. A brain MRI in August 1998 showed only mild cerebral and cerebellar atrophy. His antiretroviral regimen consisted of Viracept (Agouron Pharmaceuticals, San Diego, CA) and Combivir (Glaxo Wellcome, Research Triangle Park, NC). Routine laboratory examination was normal except for a sedimentation rate (Westergren) of 55 mm/h and elevated total cholesterol (269 mg/dL).

Cognition was intact except for some minor attentional deficits. There was marked dysarthria. His saccades were slowed, but the remainder of his cranial nerve examination was normal. He was nonfocal on pinprick and light touch testing but displayed some vibration and positional deficits. No motor weakness was noted. Conspicuous dysmetria and dysdiadochokinesis were evident. Rapid alternating movements were slow and poorly performed. A check sign, present bilaterally, was more prominent on the right. The deep tendon reflexes were normal. The plantar reflexes were flexor. His gait was broad based, and he displayed a striking inability to tandem. No chorea was noted.

The patient had been adopted and was unsure of his family history. Therefore, we undertook further evaluation for other causes of his symptoms. Lactate, ceruloplasmin levels, and thyroid functions were normal. Other tests were contemplated, however, a genetic screen for Huntington's disease (Dianon Systems, Stratford, CT) showed one normal allele with 18 repeats and an abnormal allele with 54 repeats, confirming the presence of this disorder. Subsequently, in February 1999 many aspects of his neurologic examination worsened and he developed generalized but mild chorea involving all the extremities, the face, and trunk.

In retrospect, a subtle clue to the presence of Huntington's disease had been present on the patient's brain MRI scan. This consisted of abnormal signal intensity in the putamen and caudate on the T2- and proton density–weighted images (figure). Rarely reported in some adult onset cases of Huntington's disease,[2] this finding is more common in the juvenile onset akinetic-rigid variant.[2]

Our patient with HIV-1 infection presented with symptoms typically associated with cerebellar disease. Huntington's disease is a disorder linked to abnormal expansion of a sequence of CAG nucleotide repeats on at least one allele of a gene on chromosome four. Although Huntington's disease typically presents with either affective symptoms or adventitious movements, onset with cerebellar signs and symptoms, as in our patient, has been reported in both children[3] and adults.[4] Given his initial presentation, and the presence of mild cerebellar atrophy on brain imaging, our patient clearly could have been included in the cohort presented by Tagliati et al.[1] if not for the genetic results.

We clearly are not suggesting that all patients with HIV-1 infection with cerebellar signs and symptoms have Huntington's disease. Given a prevalence of 4-to-8 per 100,000 within the population (for Huntington's disease) and about 800,000 to 1 million HIV-1–infected individuals in the United States, there ought to be only about 32 to 80 such co-afflicted individuals in the country. Although at least one other case has been discovered (Justin McArthur, MD, personal communication, April 23, 1999), their rarity would preclude so simple an explanation. However, other disorders can present with cerebellar symptoms and atrophy; a partial list would include the spinocerebellar ataxias, dentatorubral-pallidoluysian atrophy, acquired malabsorption syndromes, and some mitochondrial disorders. Some of these may be expected to occur in some patients with HIV-1 infection. Clearly the definition of a "cerebellar" syndrome regarding HIV-1 infection should be considered a diagnosis of exclusion.

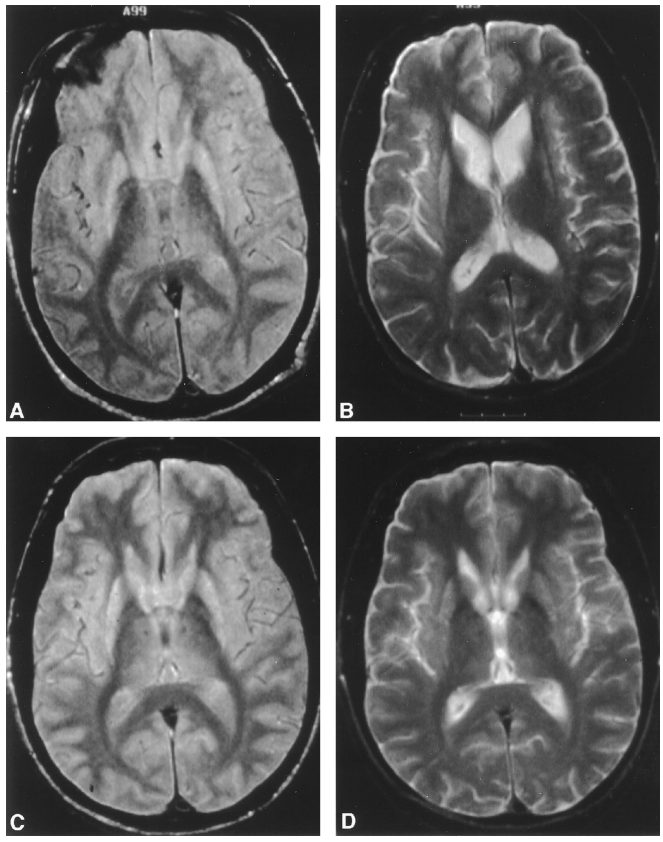

Figure. Representative sections through the striatum. Proton density–weighted images (PDWI) are on the left, and T2-weighted images are on the right. (A and B) Results of a study performed in 1998. (C and D) Similar sections from a study performed in 1995. Seen on both sets of images, but more clearly on the PDWI, is abnormal signal intensity in the putamen and caudate, reported in some cases of Huntington's disease. The apparent atrophy of the heads of the caudates (B) is caused by the cut of the section.

Gary Sclar, MD, PhD, Cheryl A. Kennedy, MD, James M. Hill, PhD, *Newark, NJ;* Michael K. McCormack, PhD, *Stratford, New Brunswick, and Piscataway, NJ*

Reply from the Authors: In describing a patient with HIV infection presenting with ataxia and dysmetria consequent to Huntington's chorea, Sclar et al. argue that isolated cerebellar disease occurring with HIV infection may simply be the result of a genetic disorder or other malady for which the patients were not tested

rather than caused by HIV infection. We agree fully with their assertion that neurologic illnesses unrelated to HIV must be considered in the patient with AIDS. Indeed, in prior publications, we have attempted to remind physicians caring for the patient with AIDS with neurologic disease not to overlook the obvious; not all disorders in this population are attributable to HIV infection.[5] Common and uncommon neurologic ailments that afflict persons without HIV infection result in disease in the HIV-infected person as well.

We described 10 patients with cerebellar disease occurring with, and likely the result of, HIV infection.[1] We were unable to detect any conclusive evidence of other microbiologic diseases, such as progressive multifocal leukoencephalopathy, nor anti-Purkinje cell antibodies as might be expected with an autoimmune paraneoplastic cerebellar degeneration. None of these patients had a family history of cerebellar disease or other movement disorders. Although the patient of Sclar et al. had Huntington's disease, this disorder is exceedingly unlikely in our population because new mutations and adult presentation with ataxia are very rare.[6] However, the possibility that the disorder resulted from complex and heterogeneous disorders unrelated to HIV infection cannot be readily dismissed in the absence of further data. Parenthetically, one of us (J.R.B.) is treating, two additional patients with a similar clinical pattern, suggesting that this cerebellar disorder is not that rare.

J.R. Berger, MD, *Lexington, KY;* M. Tagliati, MD, D. Simpson, MD, S. Morgello, MD, *New York, NY;* D. Clifford, MD, *St. Louis, MO;* R.L. Schwartz, MD, *Bronx, NY*

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Acute deterioration from thrombosis and rerupture of a giant intracranial aneurysm

To the Editor: In the Brief Communication by Khurana et al.[1] the patient was admitted to the Mayo Clinic on the first posthemorrhage day after her subarachnoid hemorrhage (SAH). It was stated that she was "mildly aphasic and obtunded," felt to be consistent with a grade III SAH, and that by the next day, she had improved to grade I. Clinical worsening was not reported thereafter for 2 more days. Why didn't this patient undergo "early surgery" for her aneurysmal subarachnoid bleed?

Roy C. Katzin, MD, *Boca Raton, FL*

Reply from the Authors: The question raised by Dr. Katzin regarding our recent report[1] is an important one and is discussed in detail in two of our studies related to rebleeding[2] and timing of surgery[3] for ruptured giant intracranial aneurysms. Although the purpose of our report was not to provide a detailed description of giant aneurysm management, it is appropriate in the context of the poor outcome in this patient to consider the planning of definitive treatment in her case. Owing to the size and location of her ruptured aneurysm, in addition to the complex arrangement of the M1 and M2 segments relative to the aneurysmal dome, endovascular treatment via balloon or coil occlusion was not a viable option. Rather, it was felt that elective surgery with provisions for intraoperative adjunctive techniques (including cardiopulmonary bypass for hypothermia and circulatory arrest) for temporary trapping and direct repair and possible reconstruction and bypass was indicated. Unfortunately, however, in the course of the necessary delay involved in arranging for these adjuncts, the patient rapidly deteriorated.

Vini G. Khurana, MD, David G. Piepgras, MD, *Rochester, MN*

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Charcot-Marie-Tooth disease type 2 with restless legs syndrome

To the Editor: Gemignani et al.[1] report a high occurrence (37%) of restless legs syndrome (RLS) in patients with Charcot-Marie-Tooth type 2 (CMT2) and none of 17 CMT1 patients. Therefore, they suggest that CMT2 may be associated with RLS. Their report is a major contribution toward identifying the neural mechanism suspected in RLS, but some points should be considered.

The occurrence of RLS and peripheral neuropathy (PN) is more common than generally believed; however, it is unclear why it is sometimes present and sometimes not present in patients affected by PN of the same etiology. We showed that axonal pathologic changes are the most frequent type of nerve damage in primary RLS,[2] and it was confirmed in patients with cryoglobulinemic neuropathy.[3] These studies suggest that axonal neuropathy is common in patients with RLS. Although axonal involvement could be a predisposing factor of RLS, the chronic course of the neuropathy also seems relevant in RLS. Gemignani et al.[1] reported that RLS was associated with positive sensory symptoms. In clinical practice when the neuropathy progressed, the positive symptoms disappeared and negative symptoms became evident. Is it the same for RLS symptoms? This is a crucial point because the cause of the usual clinical variability with waxing and waning of RLS symptoms is unknown. Unfortunately, in the report of Gemignani et al.,[1] the severity of RLS but not of neuropathy was reported, and information on the clinical course of patients with RLS followed for at least 1 year is lacking.

To our knowledge, no patients affected by acute or subacute neuropathy and RLS are reported. Our experience on a 2-year follow-up of 31 patients with PN and RLS is that all complained of chronic axonal neuropathy but of different etiology (e.g., cancer, anemia, diabetes mellitus, and cryoglobulinemia).[4] Moreover, in these patients RLS was an early symptom of neuropathy in 94% of cases (29 out of 31); however, RLS disappeared in 52% (16 out of 31) of cases who complained of a worsening of the neuropathy (unpublished data).

We believe that these clinical observations are of interest because the clinical course of RLS with neuropathy seems to be different from the RLS of suspected "central origin." Otherwise, the hypothesis that a chronic axonal neuropathy of mild or moderate degree could be a predisposing factor for RLS symptoms has to be further discussed.

S. Iannaccone, MD, A. Quattrini, MD, B. Sferrazza, MD, L. Ferini-Strambi, MD, *Milan, Italy*

Reply from the Authors: Iannaccone et al. raise interesting points about pathophysiology of RLS in peripheral neuropathy, suggesting that RLS, as well as positive sensory symptoms, is mainly related to the early phase of the disease, disappearing with worsening of neuropathy. We also noted that cryoglobulinemic neuropathy tended to be less severe when associated with RLS than in non-RLS patients.[3] Conversely, in CMT2, severity of the disease evaluated with Rankin's score was similar in RLS and non-RLS patients (range 1 to 3, median 2 in both groups) (data omitted in the revised version of the paper), and the time of appearance of RLS in the course of the disease was largely variable, ranging from 0 to 35 years (mean 5.7 ± 11.1) after the onset of CMT2.[1]

We agree with Iannaccone et al. that defining the relation of RLS with the course of neuropathy may be useful in the understanding of its pathophysiology and that the entity of nerve dam-

age may represent an important factor with respect to the occurrence, or not, of RLS in peripheral neuropathies. Axonal degeneration of moderate degree seems a necessary condition for peripheral neuropathy to develop RLS. However, cyclic recurrence and disappearance of RLS cannot be simply explained by the progression of neuropathy, but various events, including processes related to nerve degeneration and pharmacologic manipulation, may reset the RLS generator(s). RLS occurs either in association with indolent, slowly progressing axonal degeneration in CMT2[1] or with other neuropathies, such as diabetic and cryoglobulinemic,[3,4] showing variable course with active axonal degeneration alternating with quiescent periods of predominant regeneration. In addition, Rutkove et al.[5] briefly mentioned two patients with (presumably subacute) neuropathy secondary to Lyme disease, in whom RLS remitted after improvement of neuropathy.

A useful approach could consist of analyzing RLS separately in the course of different types of neuropathy, to compare manifestations of RLS with the different patterns in the evolution of nerve damage. Thus, it is expected that peripheral nerve disorder experts will add their contribution to the work of sleep and movement disorder specialists who are mainly involved in this field.[6]

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Dementia is a major predictor of death among the Italian elderly

To the Editor: We read with interest the article by Baldereschi et al. on the effect of dementia in predicting death among Italian elderly.[1]

We have pertinent data on 24 and 60 months' mortality rate obtained in a multidimensional study conducted in Italy in 1992 on a community-dwelling population 70 years of age and older.[2] All institutionalized subjects were excluded. At baseline (1992), valid questionnaires assessing demographics, mental status, chronic conditions, and functional and social status were available for 549 persons (89.6% of the eligible population). Vital status and time of death 2 (1994) and 5 years (1997) after the baseline evaluation was ascertained by telephoning patients and caregivers.

The mean age of the 549 persons (179 men and 370 women) was 76.9 ± 5.4 years. They had 4.6 ± 2.0 years of education; they were affected by 3.5 ± 2.3 chronic conditions; 134 (24.4%) lived alone; and 149 (27.1%) had one or more BADL functions lost.[3] Mini-Mental State Examination (MMSE)[4] and Geriatric Depression Scale (GDS)[5] scores were 25.2 ± 4.8 and 3.8 ± 3.2, respectively. A total of 44 and 153 persons (respectively 8% and 27.8%) died during the 2- and 5-year follow-up period. For the focus of the study, four groups based on MMSE score were defined: Group I, MMSE score 28 to 30 (n = 209); Group II, MMSE score 25 to 27 (n = 167); Group III, MMSE score 19 to 24 (n = 130); and Group IV, MMSE score <19 (n = 43). The association of MMSE groups with survival was assessed in Cox proportional hazard models. The crude risk of death controlled for age, gender, and schooling for those with a MMSE <19 was 3.9 (95% CI, 1.5 to 10.3) and 5.2 (95% CI, 3.1 to 8.9) for the 2- and 5-year follow-up period. After controlling for disability and somatic chronic diseases, both associated with mortality in bivariate Cox's model, the mortality risk for cognitively impaired was 1.5 (95% CI, 0.5 to 4.6) and 2.9 (95% CI, 1.6 to 5.4), respectively, for the 2- and 5-year follow-up period.

Although our results were obtained in a population whose mental impairment was characterized by a low MMSE (<19) and not by formal diagnosis of dementia as Baldereschi's group did, our crude mortality risk at 2 years (RR = 3.9) is comparable with that of Baldereschi et al. (RR = 3.3), whereas after controlling for disability and somatic chronic diseases, our RR is 1.5 and their's is 3.6.

One possible explanation may be the fact that our study included functional status as a confounder, whereas Baldereschi et al.'s did not. We hypothesize that at 2 years of follow-up, disability may be the best indicator that mortality is a proxy of both mental status and somatic health. On the contrary, the direct effect of dementia could be seen after a longer period of time. In fact, we found a RR of 2.9 for mortality at 5 years after baseline (corrected for confounders). The assessment of functional status has an important role in studies concerning the impact of dementia on survival.

Renzo Rozzini, MD, Tony Sabatini, MD, Piera Barbisoni, MD,
Giuseppe Bellelli, MD, Marco Trabucchi, MD, *Brescia, Italy*

Reply from the Authors: We thank Rozzini et al. for their letter that highlights a well-recognized issue: Disability is a major predictor of death in the elderly. Physical disability in older persons is related to the greater burden of chronic diseases and is considered an indicator of severity for many chronic conditions including dementia.[6,7] Data from the ILSA already shows that dementia is strongly associated with disability (OR = 5.01; 95% CI, 2.73 to 9.50) and disability increases the risk of 2-year mortality (RR = 2.77; 95% CI, 2.14 to 3.59).[8] Disability seems to be the mediator between dementia and mortality, which might be caused by the high severity level of the *disease.* Rozzini et al. do not associate dementia with short-term mortality after controlling for disability status. The explanation is that disability is far below on the causal pathway between dementia and death. Therefore, when controlling for disability, the strong association between disability and death confounds the effect of dementia. These findings support the hypothesis that the higher mortality risk in older Italians with dementia could be because of their high level of dementia-related disability.

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Contrast agent neurotoxicity presenting as subarachnoid hemorrhage

To the Editor: The article by Sharp et al.[1] on contrast agent neurotoxicity presenting as subarachnoid hemorrhage (SAH) is of great interest because it probably occurs fairly frequently. I recently had a patient with very similar presentation. The patient was transferred from a community hospital to the university hospital for the management of SAH, which turned out to be contrast agent neurotoxicity. She was an elderly woman with diabetes,

renal disease, and peripheral vascular disease (PVD), and she had a lower extremity angiogram to assess her PVD. The patient had mental status changes after the angiogram, and in her evaluation a noncontrast head CT was obtained within 24 hours of the angiogram. Like the patient described by Sharp et al., this patient also had a seizure, which incidentally happened in the CT scanner. The CT scan of the head demonstrated enhancement in the subarachnoid space and was read by the neuroradiologist as SAH, which prompted the transfer for neurosurgical care. On evaluation, the patient was comatose with absent brainstem reflexes except for brisk pupillary reflexes and had upgoing toes. The neuroradiologist at the university hospital interpreted the CT as being consistent with contrast instead of SAH. A lumbar puncture (LP) was performed to work up the altered mental status, which showed no evidence of SAH, with normal opening pressure, no xanthochromia, and elevation of RBC.

LP should have been attempted in the patient described by Sharp et al., for it would have shed light on whether the patient had a SAH. The treatment would have had to start quickly if there was a SAH. If there is significant blood in the subarachnoid space that can be seen on CT there would be signs of it on LP.[2] With supportive care and improvement in renal function, the patient fully recovered. This patient probably retained the contrast dye due to her renal disease, and the seizure may have altered the blood–brain barrier, possibly facilitating contrast into the subarachnoid space.[3] This article highlights the need to keep in mind that other procedures with contrast dye can mimic SAH on head CT.

David Y. Ko, MD, *Los Angeles, CA*

Reply from the Authors: We agree with Dr. Ko's point regarding the usefulness of LP in evaluating for SAH. Our patient had received large doses of heparin during the preceding stent procedure and had a protime of 15.7 and partial thromboplastin time of 126.1 at the time of the event. LP was considered at the time, but the risk of bleeding was believed to be significant enough to warrant holding the procedure. The possibility of her heparin-induced coagulopathy contributing to the SAH was an additional concern.

Stephen J. Sharp, MD, *Chapel Hill, NC*

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