Spinocerebellar Ataxia Type 2

Clinical Features of a Pedigree Displaying Prominent Frontal-Executive Dysfunction

Elsdon Storey, PhD; Susan M. Forrest, PhD; Janet H. Shaw, BS; Peter Mitchell, FRACR; R. J. McKinley Gardner, FRACP

Background: Spinocerebellar ataxia type 2 (SCA2) is a recently delineated cause of autosomal dominant cerebellar ataxia type I. The basic clinical neurologic features of SCA2 have been described in the literature, but neuropsychological features have not, despite statements that some patients became demented.

Objective: To describe the clinical and neuropsychological features of patients from a pedigree with SCA2.

Patients and Methods: We studied 8 affected members of an Australian pedigree of northern Italian origin with autosomal dominant cerebellar ataxia type I caused by SCA2. Patients underwent clinical neurologic examination and abbreviated neuropsychological testing, while some also underwent magnetic resonance imaging. The results were compared with pooled results from previously published studies of patients with SCA2.

Results: The pedigree displayed anticipation, with earlier onset in later generations, and there was an inverse correlation between repeat number and age at onset. The principal difference from other clinical reports of SCA2 was our finding of unequivocal frontal-executive dysfunction in 5 of 6 individuals who could be tested quantitatively, despite Mini-Mental State Examination scores in the nondemented range. This feature did not appear to correlate with either repeat size or duration of illness.

Conclusions: In light of a recent report of frontal-executive dysfunction in spinocerebellar ataxia type III, we postulate that this pattern may be common to the autosomal dominant cerebellar ataxias and frequently may be overlooked because of the insensitivity of routine screening tests such as the Mini-Mental State Examination.

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The classification of the predominantly adult-onset dominant ataxias has been revolutionized by the discovery of a number of genes, mapped or actually identified, for disorders designated as spinocerebellar ataxias (SCAs) type 1 through 7.1 Of these, the genes for SCAs 1, 2, 3, and 7 have been sequenced, and they share a common triplet repeat amplification with polyglutamine tract expansion mechanism.1 Spinocerebellar ataxia type 6 is also caused by expansion of a polyglutamine tract, but it appears to have a rather different pathogenetic basis.2

For editorial comment see page 20

Before these advances in the molecular biology of the dominant ataxias, a clinical classification proposed by Harding3 was widely used. Her autosomal dominant cerebellar ataxia type 1 (ADCA I) group consisted of pedigrees with other neurologic features in addition to ataxia (eg, dementia, ophthalmoplegia, peripheral neuropathy), except retinal degeneration. (The latter was a remarkably consistent feature in certain pedigrees and was separately designated as ADCA II, now known to correspond to SCA7.) The SCAs I through 4, and some cases of SCA6, presumably together with other SCAs whose genes are as yet unlocalized, correlate with ADCA I.

The clinical appearance now associated with SCA2 was probably first recognized as a distinct entity by Wadia and Swami,4 who described dominant ataxia with slow eye movements in families from Mumbai (formerly Bombay), India. In 1989, Orozco et al5 described a large pedigree with similar clinical features from Holguin in Cuba, which subsequently enabled localization of the responsible gene, now designated SCA2, to chromosome 12q23-24.1,6 In the same year, anticipation in an SCA2 kindred was demonstrated,7 suggesting that triplet repeat expansion might underlie this disorder. This inference received support

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SUBJECTS AND METHODS

DETECTION OF CAG EXPANSION IN SCA2 GENE

Patients had their DNA analyzed by means of the oligonucleotides SCA2-A and SCA2-B. These primers gave a product of 61 bp + 3n bp (where n equals the number of CAG repeats). Reactions contained 10 ng of genomic DNA, 0.2 mmol/L each deoxynucleotide triphosphate, 0.5 μg SCA2-A, 3.0 mmol/L magnesium sulfate, 10% dimethyl sulfoxide, and 0.5 U of Taq polymerase (Boehringer Mannheim, Mannheim, Germany) in a final volume of 20 μL. One microgram of the reverse primer, SCA2-B, was end-labeled in a kinase reaction with phosphor-33 (γ32P)-labeled deoxyadenosine triphosphate (7400 × 106 Bq/μmol). Other conditions were as recommended by the manufacturer. Thirty cycles were performed, each involving 95°C for 1 minute, 65°C for 1 minute, and 72°C for 2 minutes. An aliquot was analyzed on an 8% denaturing polyacrylamide gel. The gel was fixed, dried, and exposed for autoradiography for 48 hours at room temperature. The size of the expansion was determined relative to the M13 sequencing ladder, which was used as the molecular weight marker. Errors in estimation of triplet repeat expansion numbers were ±1 repeat in the expanded range.

NEUropsychological tests

The MMSE14 was administered in the standardized fashion, with serial 7’s used for the so-called attention section, rather than the alternative of spelling “WORLD” backward. The United Kingdom version of the National Adult Reading Test was used as an estimate of premorbid full-scale IQ and was administered and scored according to the publisher’s instructions.15 The utility of this test was well discussed by Crawford.16 Although dementia and possibly even dysarthria might lower National Adult Reading Test scores, the purpose of performing this test was to demonstrate that premorbid intelligence in our patient sample was at least within the average range. As both of these potential confounding factors would tend to lower scores, the assertion that our patients had at least average premorbid abilities (see the “Results” section) is sustainable. The F, A, S test of verbal fluency by initial letter was performed and scored as laid out by Spreen and Strauss.17 Although cerebellar dysarthria might interfere with performance on this test, the production rate was slow enough in each case (not more than 38 words in 3 minutes in any case) that pauses constituted most of the time allowed. It was judged unlikely that a slow production rate was attributable to dysarthria in any of our patients. The Victoria version of the Stroop test was administered according to the instructions of Spreen and Strauss.17 Their normative data were used for scoring, but the “W” condition (reading the ink colors of non-color-name words) was used as a control for the conflicting (“C”) condition by subtracting the z score of the former from the latter. The effect of this manipulation in this timed test is to allow for the potential reduction in visual scanning and speech production speeds in ataxic, dysarthric patients. The Wisconsin Card Sorting Test was administered and scored according to the distributor’s instructions (Psychological Assessment Resources Inc, Odessa, Fla). Categories achieved, trials to first category, total errors, perseverative responses, perseverative and non-perseverative errors, failures to maintain set, and percentage of conceptual level responses were analyzed for each subject. As it is an untimed task, with no premium on motor accuracy, its interpretation should not be confounded in this patient population.

Three bedside tests of motor regulation, based on the work of Luria,18 were used. The “conflicting tapping” test requires the patient to tap twice when the examiner taps once, and vice versa. If the patient tapped 1 for 1 and/or 2 for 2 with the examiner, despite being able to repeat the instructions afterward, the test was considered failed. Luria’s bimanual alternation (or “alternating hand movements”) test requires the patient to make a fist with one hand while opening the other, and then reverse this process, over at least 10 trials. If the patient displayed similar rather than contrary motion in the 2 hands, the test was recorded as failed. The version of Luria’s fist-palm-side (or “3-step”) test used requires patients to say the sequence as they perform it for at least 10 cycles. Persistent simplification or missequenc- ing of the target pattern was scored as a failure. Failure was also scored if the verbal sequence was correct and in conflict with each error. While all 3 tests are motor tasks, in each case the type of movement rather than its speed or accuracy was assessed, and it was considered that this was unlikely to be confounded by cerebellar motor deficits.

CLINICAL ASSESSMENT OF VESTIBULO-OCULAR REFLEX

Best-corrected visual acuity in both eyes together was established on a Snellen chart, and the head then oscillated passively through approximately 20° of yaw at approximately 2 Hz. During this oscillation, visual acuity in both eyes together was reassessed. A decrease of up to 1 line in visual acuity is considered normal,19 and a loss of 2 lines was interpreted as a borderline result. The Zee test19 was performed by observing one optic disc ophthalmoscopically, with the patient covering the other eye and attempting to fix an imaginary distant target, while the examiner oscillated the patient’s head in yaw at about 2 Hz. The disc should remain stable relative to the examiner’s line of sight if the vestibulo-ocular reflex gain is normal (approximately 0.8). If the gain is abnormally low, the disc appears to move in the opposite direction from the orbit, as the globe moves with the head. If the gain is abnormally high, the disc appears to move in the same direction as the orbit.

MAGNETIC RESONANCE IMAGING

Sagittal magnetic resonance (MR) images were obtained with a 0.3-T magnet (Fonar, Melville, NY) (echo time, 30 milliseconds; repetition time, 500 milliseconds; number of excitations, 2) for individuals IV-1 and V-1. A 1.5-T magnet (Signa, General Electric Co, Milwaukee, Wis) (echo time, 10 milliseconds; repetition time, 500 milliseconds; number of excitations, 1) was used for individual V-2.

when a 150-kd protein from affected patients was detected by Western blotting by means of a monoclonal antibody recognizing expanded polyglutamine tracts.8 Finally, the gene sequence itself was reported by 3 groups simultaneously in late 1996.9,10 and the basic molecular mechanism of a CAG expansion was con-
firmed. The range of expansion sizes on SCA2 chromosomes is 36 to 64 CAG repeats (mode, 38; mean, 41). The normal range is 14 to 31 CAG repeats, with 90% of normal chromosomes having 22 repeats and 7% having 23 repeats, while repeats of 32 to 34 CAGs compose an “intermediate range.”

We describe an Australian family of Italian extraction with ADCA I, subsequently demonstrated to be caused by SCA2. The clinical features within this pedigree are similar to those described in the literature with the exception that 5 of 6 members tested shared, to a greater or lesser extent, frontal-executive dysfunction in the presence of normal scores on the Mini-Mental State Examination (MMSE). A similar neuropsychological profile has recently been demonstrated in an SCA3 pedigree in which results of tests of learning and visual memory were normal, while deficits were shown in ability to shift attention to previously irrelevant stimulus dimensions and in the speed of visual information processing during high-demand tasks. We postulate that frontal-executive impairment, easily overlooked in the routine clinical setting, may be a common feature of the ADCAs.

RESULTS

PEDIGREE AND RESULTS OF SCA2 GENE TESTING

The pedigree of the family is shown in Figure 1, and the molecular analysis of the SCA2 CAG expansion in 6 of the 8 tested individuals is shown in Figure 2. Our study is restricted to the Australian branch of the family, the descendants of individual II-1. We noted a tight inverse correlation between CAG repeat number and reported age at onset (Figure 3), especially for repeat numbers of less than 40 to 42, an observation that is well documented in larger studies. As is also consonant with

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**Figure 1.** Pedigree of the family, excluding descendants of presumed unaffected members. Solid symbols indicate known or presumed affected members. Individuals with asterisks were personally examined; subject IV-3 died soon thereafter. Information on the clinical state of other members is anecdotal. Bull’s-eye symbol indicates asymptomatic obligate heterozygote. Deceased status (diagonal line) shown for the Australian branch (descendants of subject II-1) only.

**Figure 2.** Detection of CAG expansion in affected individuals. Track 1, Individual IV-9, 22 of 38 repeats; track 2, individual IV-1, 22 of 39 repeats; track 3, individual V-1, 22 of 40 repeats; track 4, individual V-2, 22 of 44 repeats; track 5, individual IV-3, 22 of 41 repeats; and track 6, individual V-5, 23 of 47 repeats.

**Figure 3.** Scatterplot diagram showing the inverse relationship between CAG repeat number and age at onset. This was significant, with a Spearman rank correlation coefficient of 0.83 and a 2-tailed P value of .02 (exact significance for n = 8).
the observations of others, the present pedigree appears to display anticipation. Three child-parent pairs (IV-1 and V-1, IV-3 and V-5, and IV-9 and V-13) had recorded ages at onset, and the ages in the children were younger than the parents by 14, 11, and 26 years, respectively. These 3 pairs show increases in repeat size from parent to child to display anticipation. Three child-parent pairs (IV-1 and V-1, IV-3 and V-5, and IV-9 and V-13) had recorded ages at onset, and the ages in the children were younger than the parents by 14, 11, and 26 years, respectively. These 3 pairs show increases in repeat size from parent to child 

**CLINICAL FEATURES**

The clinical features of the pedigree are shown in Table 1. The average age at onset was 33.5 years (range, 21-46 years), and the duration of illness when the person was examined ranged from 4 to 20 years. One individual, IV-3, died after being examined but before this article was prepared. The pattern of clinical findings in our pedigree matches that in the literature. However, with the possible exception of ocular apraxia.‡ Impossible to assess; patient anarthric and apparently demented. †Ocular apraxia.

Table 1. Clinical Features of Spinocerebellar Ataxia Type 2 Pedigree

<table>
<thead>
<tr>
<th>Pedigree Member</th>
<th>Repeat No. of Expanded Allele</th>
<th>Age at Onset, y</th>
<th>Duration of Illness When Examined, y</th>
<th>Slow Saccades</th>
<th>Reflexes*</th>
<th>Vibration Sense at Toes</th>
<th>Perioral Fasciculations</th>
<th>Postural Tremor</th>
<th>Dysphagia</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV-1</td>
<td>39</td>
<td>45</td>
<td>12</td>
<td>++</td>
<td>Normal</td>
<td>Normal</td>
<td></td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>IV-3</td>
<td>41</td>
<td>32</td>
<td>20</td>
<td>++++</td>
<td>KJ, AJ absent</td>
<td>Normal</td>
<td>AJ brisk</td>
<td>Normal</td>
<td>++</td>
</tr>
<tr>
<td>IV-7</td>
<td>42</td>
<td>28</td>
<td>10</td>
<td>+++</td>
<td>AJ brisk</td>
<td>Normal</td>
<td>AJ brisk</td>
<td>Normal</td>
<td>++</td>
</tr>
<tr>
<td>IV-9</td>
<td>37</td>
<td>56</td>
<td>10</td>
<td>+</td>
<td>Normal</td>
<td>Normal</td>
<td>AJ brisk</td>
<td>Normal</td>
<td>++</td>
</tr>
<tr>
<td>V-1</td>
<td>40</td>
<td>31</td>
<td>5</td>
<td>+</td>
<td>KJ brisk</td>
<td>Normal</td>
<td>Isometric tremor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V-5</td>
<td>44</td>
<td>25</td>
<td>4</td>
<td>+++</td>
<td>KJ, AJ absent</td>
<td>Normal</td>
<td>None</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>V-7</td>
<td>47</td>
<td>21</td>
<td>8</td>
<td>+++</td>
<td>AJ absent</td>
<td>Normal§</td>
<td>+ Limbs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V-9</td>
<td>37</td>
<td>21</td>
<td>8</td>
<td>+</td>
<td>Normal</td>
<td>Normal§</td>
<td>Trunk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V-13</td>
<td>38</td>
<td>30</td>
<td>5</td>
<td>±</td>
<td>Normal</td>
<td>Normal</td>
<td>None</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* KJ indicates knee jerk; AJ, ankle jerk; ±, questionable; +, mild; ++, moderate; and ++++, severe.
† Ocular apraxia.
‡ Impossible to assess; patient anarthric and apparently demented.

Table 2. Pattern of Clinical Findings in Relation to Published Series

<table>
<thead>
<tr>
<th>Examination Findings</th>
<th>Pooled Series % With Finding</th>
<th>Total No. of Patients</th>
<th>Current Series, % (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow saccades</td>
<td>68</td>
<td>492</td>
<td>63*</td>
</tr>
<tr>
<td>Lower-limb hyperreflexia</td>
<td>53</td>
<td>475</td>
<td>38</td>
</tr>
<tr>
<td>Lower-limb hyperreflexia</td>
<td>25</td>
<td>475</td>
<td>25</td>
</tr>
<tr>
<td>Impaired vibration sense (lower limbs)</td>
<td>32</td>
<td>459</td>
<td>0</td>
</tr>
<tr>
<td>Perioral or lingual myokymia or fasciculations</td>
<td>43</td>
<td>206</td>
<td>38</td>
</tr>
<tr>
<td>Postural tremor</td>
<td>46</td>
<td>445</td>
<td>50</td>
</tr>
</tbody>
</table>

* Or 88% if patients with slight slowing are included.

Of course, ataxia was virtually universal and indeed was the defining feature for inclusion as “affected” in our pedigree. In addition, the symptom of dysphagia was reported in 45% of the 198 cases from the pooled series in which this information was recorded and in 4 (50%) of our own series. It can be seen that, with the exception of vibratory sense loss in the lower limbs, the clinical findings in our pedigree closely reflect those in the literature. However, with the possible exception of ocular apraxia and the other features reported in Table 2 have not proved reliable in distinguishing between the various ADCA I genotypes.

**EYE MOVEMENTS AND NEUROIMAGING**

The results of clinical assessment of eye movements are shown in Table 3. It is notable that no patient complained of spontaneous or movement-induced oscillopsia on inquiry, and no patient had spontaneous nystagmus with fixation while sitting erect, although 1 (individual V-5) developed downbeating nystagmus and vertigo on attempting to lie flat (supine) for MR imaging. In this context, the sagittal MR images in the 3 of our patients in whom they were obtained (IV-1, V-1, and V-2; Figure 4) are of interest. Atrophy of cerebellar hemispheres, vermis, middle cerebellar peduncles, and medulla and upper spinal cord were present in each case. It can also be seen that the 2 patients with SCA2 who had marked saccadic slowing (IV-1 and V-2) had more severe pontine atrophy and more marked cerebellar vermis atrophy than patient V-1. In both cases the inferior vermis was more atrophic than the superior. Although sparing of the flocculonodular lobe has been reported pathologically in SCA, the resolution of these scans was insufficient to establish such sparing in our patients.

**NEUROPSYCHOLOGICAL FEATURES**

The results of limited neuropsychological testing of these patients is shown in Table 4. In the 6 in whom it could be assessed with the National Adult Reading Test, esti-
mated premorbid IQ was within the average range. The MMSE was above the usual cutoff (of 24) in all 7 patients who consented to its performance. Despite this, of the 6 in whom standardized tests assessing some aspect of frontal-executive function were performed, 5 were at 4 SDs below the published means for controls matched for age, sex, and educational attainment on at least 1 measure. Of the measures used, uncorrected error rate on the conflicting portion of the Stroop test was the most consistently and severely abnormal (Table 4). This is not a measure that would be expected a priori to be impaired as a consequence of cerebellar-related motor deficit. Of the 7 affected individuals in whom Luria’s motor regulation tasks were administered, 5 failed at least 1 of these 3 tasks (Table 4). Interestingly, each of the 3 tasks was passed by at least 1 patient who failed at least 1 of the others, which would not have been expected had 1 or more been confounded by the patients’ shared cerebellar motor deficit. Three individuals also displayed behavior that was judged subjectively to be impulsive. Indeed, it was this observation in individual V-2 that led to the systematic investigation of all testable, consenting family members.

**COMMENT**

**NEUROTOLOGIC AND NEURORADIOLOGICAL CHARACTERISTICS**

Of the published series of patients with SCA2, only 1 addressed the vestibulo-ocular reflex gain. It was found to be impaired in 10 of 14 patients, although the assessment method used was not stated. We found no evidence of nystagmus, and little evidence of abnormal vestibulo-ocular reflex gain, in any of our patients with the use of 2 simple bedside tests. This is in marked contrast to the findings in some other cerebellar cortical degenerations, such as SCA6. It is tempting to speculate that the relative sparing of the flocculonodular lobe described neuropathologically underlies the relative scarcity of “cerebellar” eye movement disorders in SCA2; disease of this portion of the cerebellum appears to underlie many of these abnormalities of ocular motility. Unfortunately, the resolution of the MR images available to us was insufficient to demonstrate sparing of the archicerebellum. As has been pointed out recently by Burk et al, the typical patient with SCA2 displays global cerebellar and pontine atrophy, which reflects the reported pathological features, and may aid differentiation from SCA3. The results of MR imaging in our patients with SCA2 conform to their findings.

**NEUROPSYCHOLOGICAL FEATURES**

The clinical features of SCA2 in 111 patients from 32 families have recently been tabulated, with a reported frequency of “mental deterioration” of 14%, including 4% who displayed only “memory loss.” This was in contrast to the findings in the original Cuban pedigree, where “dementia” occurred in only 1 of 263 affected pedigree members. Subsequent reports of other pedigrees between 1993 and 1995, comprising 98 patients in total, failed to mention cognitive impairment or dementia as a feature of SCA2. Du¨r re ta l reported 3 SCA2 pedigrees from Martinique, with dementia occurring in only 1 of these families. Geschwind et al noted dementia in 6 of their 16 American patients with SCA2, apparently all from the same early-onset African American pedigree. The nature of the dementia was not specified in the report but consisted of a history indicative of frontal-subcortical dementia, progressing rapidly to global dementia that had supervened in each case before assessment could be undertaken (Dan Geschwind, MD, PhD, written communication, March 1998). Schols et al recently reported that “mild dementia was suspected clinically in 5 [of 21 SCA2] patients,” with “poor memory, concentration problems, deficits in cognitive function, and emotional instability.” Cancel et al related “memory loss or dementia” in patients with SCA2 to duration of illness; those without such impairment had a mean disease duration of 10.8 ± 7.0 years, whereas those with these features had a mean disease duration of 17.3 ± 9.0 years. There was no correlation with CAG repeat length, and

<table>
<thead>
<tr>
<th>Table 3. Clinical Assessment of Eye Movements*</th>
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<tbody>
<tr>
<td>Pedigree Member</td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>IV-1</td>
</tr>
<tr>
<td>IV-3</td>
</tr>
<tr>
<td>IV-7</td>
</tr>
<tr>
<td>IV-9</td>
</tr>
<tr>
<td>V-1</td>
</tr>
<tr>
<td>V-2</td>
</tr>
<tr>
<td>V-5</td>
</tr>
<tr>
<td>V-13</td>
</tr>
</tbody>
</table>

*VOR indicates vestibulo-ocular reflex; NT, not tested; N, normal; ?, impossible to assess (patient apparently demented, with oculomotor apraxia); ±, questionable; +, mild; ++, moderate; and ++++, severe.
†Optokinetic nystagmus lost vertically.
‡No effective saccades; ocular apraxia.
§Visual suppression of VOR gain normal.
||Positional downbeat nystagmus on lying prone only; none when vertical.

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no mention was made of a correlation with ataxia severity, which is likely to depend on both CAG repeat length and duration of illness. Kish et al \(^\text{35}\) had previously reported that the degree of cognitive impairment correlated with ataxia severity in a heterogeneous group of patients with SCA. \(^\text{35}\) Interestingly, this impairment involved executive control, with behavior that endangered self and others. Frontal-executive dysfunction was strongly suspected but could not be unequivocally confirmed, as she declined testing. This interaction stimulated us to look more closely at the remaining pedigree members. In keeping with the tenor of most previous reports, none had an MMSE score below 25 and might therefore have been classified as nondemented, even if clinical assessment had included this simple global measure. However, all except individual IV-1 produced clearly abnormal results on at least 1 of the verbal fluency (F, A, S), modified Stroop (error rate), and Wisconsin Card Sorting tests. The last is independent of output speed, and the Stroop test can be rendered so by subtracting the non-conflicting from the conflicting condition. In addition, 4 of 6 subjects produced at least 1 abnormal qualitative result on Luria’s tests of motor regulation. Although such tests might be thought to be invalidated by cerebellar motor dysfunction, they are untimed, and movement type rather than movement accuracy is assessed. In addition, although all patients had various degrees of severity of the same motor deficit, there was no hierarchical pattern of failure on these tests. Both of these factors suggest that the results of such testing are valid in this patient population. We suggest that frontal-executive dysfunction may be common in SCA2 and is perhaps currently being overlooked, as it can be present in the absence of overt dementia. Patients from different family and ethnic backgrounds need to be tested to confirm this conclusion, however, especially in view of the reported interfamily variation in dementia rates in SCA2, and as it is unclear whether the frontal-executive dysfunction reported herein represents a milder form of SCA2 dementia or an independently occurring entity.

The disparity between MMSE scores and results of frontal-executive function testing is hardly surprising: the MMSE is notably insensitive to impairment of such functions (eg, see Royall et al \(^\text{36}\)). This result should simply serve to alert clinicians who care for these patients that the frequency of cognitive impairment may previously have been underestimated in SCA2, and to reinforce the dictum that a normal MMSE score does not guarantee a cognitively intact patient.

Perhaps of more interest is that the frontal-executive dysfunction documented in this study helps to advance the case for such deficits being common to the patients with ADCA as a group. \(^\text{13,35}\) Indeed, there has been increasing interest of late in the possibility of a significant cerebellar contribution to cognition, \(^\text{37}\) and although the field is beset by controversy, \(^\text{38-40}\) a recent review has concluded that it is increasingly difficult to ignore the weight of evidence from converging methods, including functional imaging studies in normal individu-

Figure 4. Sagittal magnetic resonance images of patients IV-1 (A), V-1 (B), and V-2 (C). Sagittal sequences best show the pontine, medullary, and vermian changes; note particularly the flattening of the anterior surface of the pons and considerable increase in the volume of the prepontine cistern and cisterna magna.
als, in favor of the cerebellum playing such a role. While a broad range of tasks has been investigated in patients with cerebellar dysfunction, Fiez characterized those to which the cerebellum seems to contribute as being “initially effortful and in which correct responses are self-discovered (typically through trial and error), but that are performed more automatically (more smoothly, quickly and accurately) following practice.” It is easy to envisage how disruption of such a system for learning novel tasks could result in impairment of the ability to perform the Wisconsin Card Sorting Test, to suppress usual responses in favor of novel responses efficiently in the modified Stroop test, or to search the lexicon in a novel fashion in the F, A, S test. In other words, cerebellar dysfunction might result in a “frontal-executive dysfunction” syndrome. However, the burden of neuronal loss in SCA2, as for the other causes of ADCAs I and II, is not confined to the cerebellum. Maruff et al speculated that the deficits that they documented in SCA3 (Machado-Joseph disease) were caused by disruption of frontal-subcortical systems, and neuropathological findings in the few cases of SCA2 where they have been reported show that while the pallidolysian system is much less severely involved than in SCA3, the substantia nigra is involved in both. Therefore, it is also possible that the frontal-executive dysfunction in our patients with SCA2 has a cause not directly related to their cerebellar abnormality, and its presence does not contribute strongly to the debate. In this regard, a careful neuropsychological study of patients with SCA6 (where the neuronal damage is more closely confined to the cerebellar cortex and inferior olive) may be informative and should be undertaken.

The relationship between repeat number and degree of frontal-executive dysfunction is not capable of formal analysis in this study, as all but 1 of the 6 affected family members assessed showed evidence of frontal-executive impairment, and as no single or composite scale of frontal-executive dysfunction was used. Nevertheless, there is no clear correlation between repeat number and the results of individual tests of frontal-executive function. This extends the findings of Cancel et al in this regard, who found no clear correlation between dementia and repeat number in SCA2.

NOTE ADDED IN PROOF

In addition, since submission of this manuscript, Gambardella et al have reported early and selective impairment of performance on the Wisconsin Card Sorting Test in 3 Italian families with SCA2.

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REFERENCES