

Selective sparing of pain pathways in a patient with adult cerebral adrenoleukodystrophy

A. Romaniello, MD; A. Aversa, MD; G. Cruccu, MD;
M. Leandri, MD; and M. Manfredi, MD

Adrenoleukodystrophy (ALD) is a metabolic disease inherited as an X-linked recessive trait. An enzymatic defect in subcellular peroxisomal degradation causes an accumulation of saturated very-long-chain fatty acids. Current classifications distinguish several variants: presymptomatic or asymptomatic ALD, childhood cerebral ALD, adolescent cerebral ALD, adult cerebral ALD, adrenomyeloneuropathy, and "Addison only" ALD.¹ The predominant feature in ALD is cerebral white matter involvement with widespread demyelination. Most patients present clinically with spastic paraplegia, urinary incontinence, and epileptic seizures; in patients with adrenomyeloneuropathy, signs of myelopathy and peripheral nerve involvement dominate the clinical course. A frequent feature is adrenal gland insufficiency. In adult patients with ALD the diagnosis relies on plasma assay of very-long-chain fatty acids and neuroradiologic and neurophysiologic evidence of cerebral white matter involvement.^{1,2}

For the first time in a case of ALD, we report a study of central nociceptive pathways, by means of laser evoked potentials.

Case report. A 22-year-old man presented because of difficulty in walking. Clinical examination showed a bronzed skin with hyperpigmentation of the gums and palms; weakness; pyramidal signs; mild ataxia in the four limbs; mild cognitive disturbances; and normal somatosensory, visual, and hearing systems. The endocrinologic evaluation showed primary adrenal insufficiency and subclinical primary testicular dysfunction. Thyroid function was normal. Biochemical studies showed a significant increase in very-long-chain fatty acids (C24: 66.34; C26: 2.56 $\mu\text{mol/L}$; C24/C22: 1.776; C26/C22: 0.068).

Results of peripheral nerve conduction studies were normal. Motor evoked potentials (MEPs) after transcranial magnetic stimulation, somatosensory evoked potentials (SEPs), visual evoked potentials (VEPs), and brainstem auditory evoked potentials (BAEPs) all disclosed a marked slowing of central conduction. Laser evoked potentials (LEPs) were obtained by delivering brief radiant heat pulses to the dorsum of the hand and foot by means of a CO₂ laser stimulator (wavelength 10.6 μm , intensity 1.5 to 15 W, duration 10 to 15 msec, beam diameter 2.5 mm),³ and were recorded from the vertex.^{3,4} Latency and amplitude values of hand LEPs (N230, P295, 19 μV) and foot LEPs (N310, P380, 15 μV) were similar to those commonly found in normal subjects,⁴ and within the normal limits of our laboratory (figure).

Cranial MRI (see the figure) showed a butterfly-shaped area of increased signal intensity involving the anterior portion of the corpus callosum and the white matter of both frontal lobes; the white matter lesion extended caudally to the cerebral peduncles. Results of spinal MRI scans were normal.

Treatment with a low-fat diet and Lorenzo's oil² started after diagnosis returned plasma very-long-chain fatty acids to normal levels within 3 months. Nevertheless, clinical and neurophysiologic assessment at 12 and 18 months after starting therapy showed a progressive worsening of spasticity and ataxia, and a further increase of central conduction times, with absent lower-limb MEPs and SEPs, in the evoked potential studies. Only the LEPs remained normal throughout the follow-up.

Discussion. The patient we observed presented with an infrequent distribution of MRI abnormalities. Instead of the posterior lobe white matter changes more typical of the classic forms of ALD, our patient had predominantly frontal lesions¹ extending caudally to the cerebral peduncles. Consistently, impairment of the corticospinal pathways entailed a motor dysfunction and severe MEP abnormalities. The abnormal SEPs, VEPs, and BAEPs, however, disclosed subclinical dysfunction in the posterior lobes and brainstem. Histopathologic studies in the cerebral variant of ALD usually describe demyelination as varying in degree and distribution.⁵ Partial myelin damage may not be revealed by MRI

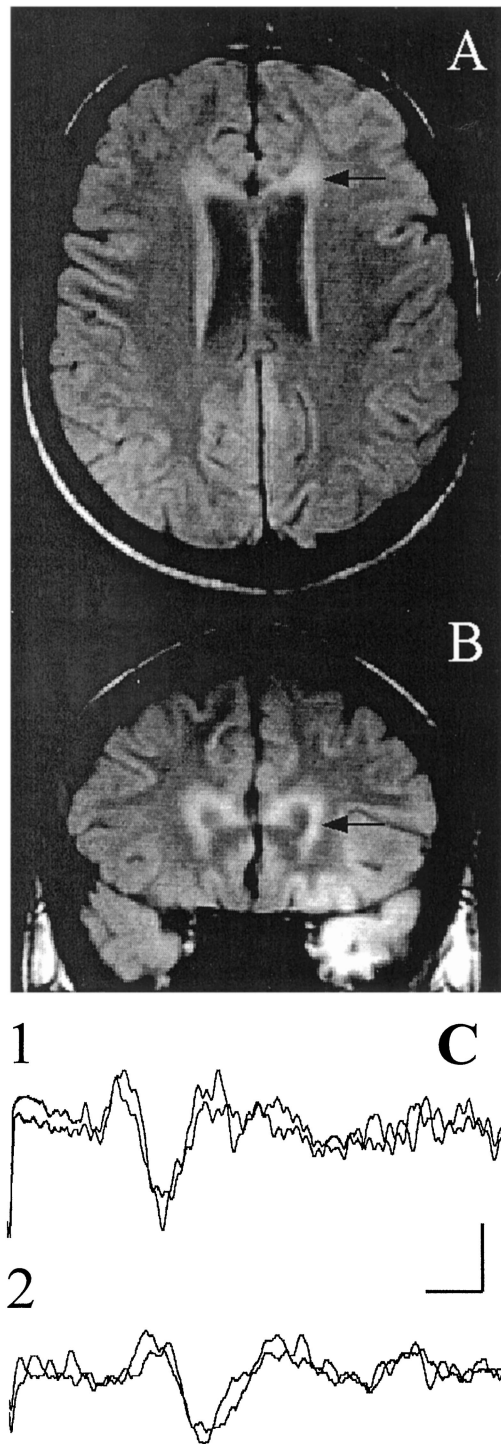


Figure. Axial (A) and coronal (B) proton density-weighted MRI scans show a butterfly-shaped area of abnormal signal (arrows). Laser evoked potentials after hand (C1) and foot (C2) stimulations. Two averages of 12 trials superimposed. Negativity upward. Calibration 100 msec, 10 μV .

and could explain our patient's abnormal results in multimodality evoked potential studies.^{2,5}

Surprisingly, only the LEPs remained normal throughout the follow-up, either because of the anatomic course of pain pathways or because of the characteristics of pain fibers. Our multimodality evoked potential study demonstrated a diffuse white matter impairment, as expected in the cerebral forms. Furthermore, the butterfly-shaped area of abnormal MRI signal (see the figure)

included part of the white matter below the anterior cingulate. This area has been indicated by PET studies as one of the main targets of the experimental hot pain input⁶ and by source analysis studies as the generator of the main components of the LEP.⁷ Hence the spared nociceptive function as opposed to the altered motor, somatosensory, visual, and acoustic potentials could depend on structural differences in the myelin sheaths rather than the anatomic course of pain pathways. LEPs, as well as hot pain, are mediated by small fibers both in the peripheral and central nervous systems. We propose that in cerebral ALD the demyelinating process damages more severely the fibers with large myelin sheaths while sparing the smaller myelinated fibers, as observed in peripheral nerves of patients with adrenomyeloneuropathy.

Key words: Adrenoleukodystrophy—Laser evoked potentials.

From the Departments of Neurological Sciences (Drs. Romaniello, Cruccu, and Manfredi) and Medical Pathophysiology (Dr. Aversa), University "La Sapienza," Rome; Inter-university Center for the Neurophysiology of Pain (CIND) (Drs. Cruccu and Leandri), Genova; and IRCCS Neuromed (Dr. Manfredi), Pozzilli, Italy.

Received June 2, 1999. Accepted in final form August 31, 1999.

Address correspondence and reprint requests to Dr. Giorgio Cruccu, Dipartimento Scienze Neurologiche, Viale Università 30, 00185 Rome, Italy.

Copyright © 2000 by the American Academy of Neurology

References

- van Geel BM, Assies J, Wanders RJ, Barth PG. X-linked adrenoleukodystrophy: clinical presentation, diagnosis, and therapy. *J Neurol Neurosurg Psychiatry* 1997;63:4–14.
- Restuccia D, Di Lazzaro V, Valeriani M, et al. Neurophysiologic follow-up of long-term dietary treatment in adult-onset adrenoleukodystrophy. *Neurology* 1999;52:810–816.
- Cruccu G, Romaniello A, Amantini A, Lombardi M, Innocenti P, Manfredi M. Assessment of trigeminal small-fiber function: brain and reflex responses evoked by CO₂-laser stimulation. *Muscle Nerve* 1999;22:508–516.
- Kakigi R, Shibasaki H, Ikeda A. Pain-related somatosensory evoked potentials following CO₂ laser stimulation in man. *Electroencephalogr Clin Neurophysiol* 1989;74:139–146.
- Schaumburg HH, Powers JM, Raine CS, Suzuki K, Richardson EP Jr. Adrenoleukodystrophy: a clinical and pathological study of 17 cases. *Arch Neurol* 1975;32:577–591.
- Talbot JD, Marrett S, Evans AC, Meyer E, Bushnell MC, Duncan GH. Multiple representations of pain in human cerebral cortex. *Science* 1991;251:1355–1358.
- Chen ACN, Bromm B. Pain-related generators of laser-evoked brain potentials: brain mapping and dipole modelling. In: Bromm B, Desmedt JE, eds. *Advances in pain research and therapy*. Vol. 22. New York: Raven, 1995:245–266.

Dystrophinopathy expressing as either cardiomyopathy or Becker dystrophy in the same family

L. Palmucci, MD; T. Mongini, MD; L. Chiadò-Piat, PhD; C. Doriguzzi, MD; and A. Fubini, MD

Dystrophinopathies include different conditions caused by alterations of the Xp21 gene. The clinical spectrum encompasses the typical Duchenne phenotype: early onset muscular weakness; loss of ambulation by 12 years of age and severe progression, with death in the second or third decade; and the more slowly progressive Becker muscular dystrophy, often with a normal life span. Recently, other presentations have been described, including exercise intolerance with muscle cramps and myoglobinuria, late-onset benign muscle weakness, isolated increase of serum creatine kinase (CK), and congestive cardiomyopathy without muscle weakness.¹ Although the correspondence between the phenotype and the molecular alteration is not absolute, the clinical expression of dystrophinopathies in affected members of single families carrying the same mutation is usually similar.²

Case report. A 65-year-old man (figure, A; II-2) presented to us following the incidental finding of increased serum CK in his 5-year-old grandson (figure, A; IV-2). He had a family history of "cardiomyopathy," which caused the death of his mother (figure, A; I-1) and two brothers (figure, A; II-3, II-4) in their sixth decade. He had two healthy daughters; one of them (figure, A; III-2) had two sons, 5 and 8 years old. The patient reported normal motor development; denied cramps, myalgias, and fatigability; and had been well until 5 years before, when a congestive cardiomyopathy had been diagnosed. Neurologic examination showed normal muscle strength and no trophic changes. Results of laboratory examination were normal, including serum CK. Echocardiography showed severe dilation of the left ventricle with reduced ejection fraction and mitral and aortic regurgitation. Coronary arteriography showed very mild atherosclerosis without significant obstructive lesions. Results of electromyography (EMG) were normal. Results of quadriceps muscle biopsy were normal apart from occasional small fibers and some internal nuclei. Monoclonal antibodies against the N-terminal, C-terminal, and rod domain of dystrophin (Novocastra Laboratories; Newcastle-upon-Tyne, UK) showed normal sarcolemmal distribution of the protein around the contour of muscle fibers and moderate quantitative reduction. Western blotting demonstrated reduced molecular weight of dystrophin (figure, B). Monoclonal antibodies against alpha-sarcoglycan, beta-sarcoglycan, gamma-sarcoglycan, spectrin (Novocastra Laboratories), and merosin (Chemicon; Temecula, CA)

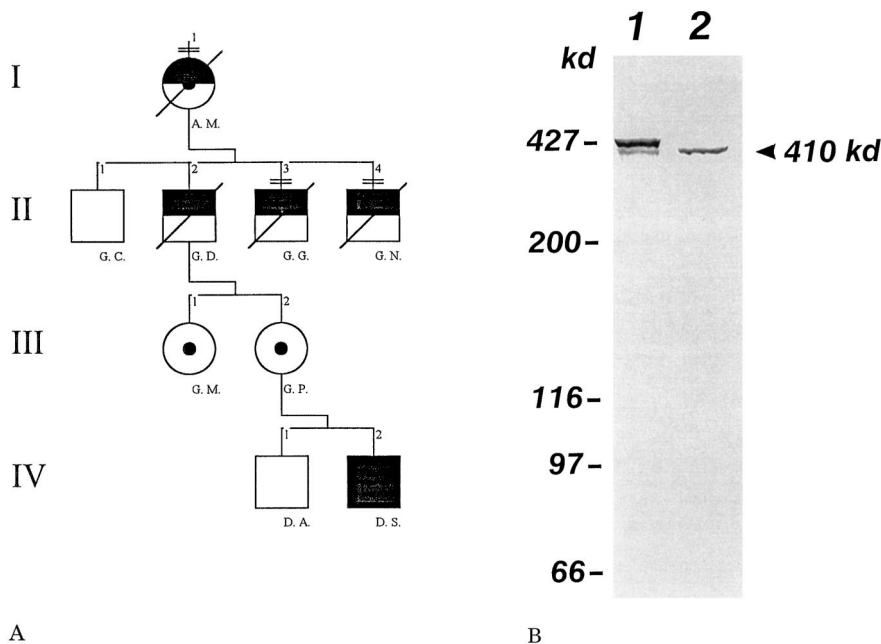


Figure. (A) Pedigree of the family. Female, dotted, half black: heterozygote with cardiomyopathy; female, dotted: heterozygote with normal creatine kinase; male, half black: cardiomyopathy; male, full black: Becker muscular dystrophy. (B) Western blotting shows reduced molecular weight of dystrophin. Lane 1: normal subject; lane 2: our patient with cardiomyopathy.

showed normal distribution of the proteins. Multiplex PCR analysis indicated a deletion of exons 48–51 of the Xp21 gene.

The patient's daughters, obligate carriers of the mutation, and the elder grandson (figure, A; IV-1) had normal results on neurologic examination, serum CK, ECG, and echocardiography. The 5-year-old grandson had calf hypertrophy and mild proximal muscle weakness. Serum CK was 3,000 U/L (normal values up to 190). PCR analysis detected the same deletion as in his grandfather. Results of echocardiography were normal. PCR analysis was also performed in his brother and detected no deletions.

The patient died suddenly of cardiac arrest at age 68; his grandson, now age 9, shows slight progression of the muscle weakness.

Discussion. Congestive cardiomyopathy is a frequent complication of Xp21 muscular dystrophy. Its occurrence in the absence of muscle weakness,³ even in female carriers, is now common knowledge, and it is associated with a wide range of molecular alterations,^{4,5} including promoter mutations.⁵ Although muscle involvement in these patients remains subclinical, the presence of increased serum CK is a constant clue and, when associated with congestive cardiomyopathy, it suggests an underlying muscle pathology and should prompt dystrophin study. Conversely, in the current patient normal serum CK and EMG seemed to exclude a myopathy; muscle biopsy was motivated by hyperCKemia in the patient's grandson and by family history suggesting X-linked transmission. Paralleling normal CK, muscle tissue was nearly normal and only Western blotting could unequivocally demonstrate dystrophin alteration. It is not known whether the patient had increased CK when younger and we cannot exclude that the normal CK found at age 65 resulted from reduced skeletal muscle usage due to age and cardiopathy.

The association in our patient of nonatherosclerotic cardiomyopathy and dystrophinopathy and the presence of family history of fatal X-linked cardiomyopathy in the sixth decade argues for an etiologic correlation between the gene deletion and the heart pathology. We can reasonably suppose that the patient's mother was a carrier with prevalent cardiac involvement; the two daughters, obligate carriers of the deletion, are currently too young to exclude a possible heart involvement in the future.

Prevalent, but not exclusive, cardiac involvement has been observed in rare cases with deletions involving exons 45–48⁶ or 48–49.⁷ Isolated cardiomyopathy without skeletal muscle involvement, apart from increased serum CK, has been observed in patients with mutations selectively affecting the heart dystrophin.⁵ The interest of our case lies in the absence of skeletal muscle involvement (normal neurologic examination, serum CK, and EMG), despite reduced weight of dystrophin and a deletion usually causing a Becker phenotype, as in the patient's grandchild. Normal CK, therefore, may not be sufficient to exclude dystrophinopathy in isolated congestive cardiomyopathy. Another intriguing finding is the different phenotype of the same gene mutation in different members of the same family: isolated congestive cardiomyopathy in the grandfather and typical Becker phenotype in the grandson. This could indicate that individual factors can modulate the expression of the genotype.

Key words: Xp21 muscular dystrophy—Cardiomyopathy—Muscle biopsy—DNA analysis.

From the Paolo Peirola Center for Neuromuscular Diseases (Drs. Palmucci, Mongini, Chiadò-Piat, and Doriguzzi), Department of Neurosciences, and the Department of Internal Medicine (Dr. Fubini), University of Turin, Italy.

Supported by Telethon, Grant 1011, and MURST, ex-60%.

Received June 10, 1999. Accepted in final form September 6, 1999.

Address correspondence and reprint requests to Dr. Laura Palmucci, Centro per le Malattie Neuromuscolari, via Cherasco, 15, I-10126 Torino, Italy.

Copyright © 2000 by the American Academy of Neurology

References

1. Doriguzzi C, Palmucci L, Mongini T, Chiadò-Piat L, Maniscalco M, Resagno G. Systematic use of dystrophin testing in muscle biopsies: results in 201 cases. *Eur J Clin Invest* 1997;27:352–358.
2. Angelini C, Fanin M, Freda MP, et al. Prognostic factors in mild dystrophinopathies. *J Neurol Sci* 1996;142:70–78.
3. Palmucci L, Doriguzzi C, Mongini T, et al. Dilating cardiomyopathy as the expression of Xp21 Becker type muscular dystrophy. *J Neurol Sci* 1992;111:218–221.
4. Oldfors A, Eriksson BO, Kyllerman M, Martinsson T, Wahlstrom J.

Dilated cardiomyopathy and the dystrophin gene: an illustrated review. *Br Heart J* 1994;72:344–348.

5. Ferlini A, Galié N, Merlini L, Sewry C, Branzi A, Muntoni F. A novel *Alu*-like element rearranged in the dystrophin gene causes a splicing mutation in a family with X-linked dilated cardiomyopathy. *Am J Hum Genet* 1998;63:436–446.
6. Siciliano G, Fanin M, Angelini C, et al. Prevalent cardiac involvement in dystrophin Becker type mutation. *Neuromusc Disord* 1994;4:381–386.
7. Muntoni F, Di Lenarda A, Porcu M, et al. Dystrophin gene abnormalities in two patients with idiopathic dilated cardiomyopathy. *Heart* 1997;78:608–612.

Pupillary diameter assessment: Need for a graded scale

I. Litvan, MD; G. Saposnik, MD; J. Mauriño, MD; L. Gonzalez, MD; R. Saizar, MD; R.E.P. Sica, MD; and J.J. Bartko, PhD

Assessment of pupillary diameter is useful for lesion location, a necessary step in diagnosing neurologic disorders.^{1,2} Recognition of pupillary changes can serve as an early warning of acute brain injury, and may, with prompt treatment, prevent further injury. However, not all pupillary changes are relevant, because size changes in various physiologic or pharmacologic conditions.¹

A few studies have evaluated the reliability of nurses to assess pupils,^{3,4} but none evaluated the reliability of physicians. Because, in practice, physicians usually use their own impression to assess pupillary diameter, we questioned if such a practice is justified. In this study, the inter- and intrarater reliability of physicians assessing pupillary diameters using their own judgment or a graded scale was evaluated.

Methods. Four third- and fourth-year neurology residents consecutively evaluated the pupil size of 100 subjects (60% men; median age, 41.5 years) in randomized order. Subjects gave informed consent. Raters assessed pupil diameter twice with a 20-minute difference between trials. Room conditions including light were constant. Raters were unfamiliar with the subjects they examined. Raters 1 and 2 assessed pupil size using a graded scale; Raters 3 and 4 assessed pupil size subjectively. The scale, adapted from the French catheter scale (Cordis, Miami, FL), is graduated in 0.3-mm increments (from 1 to 11.3 mm) and has perforated circles rather than filled circles of different sizes. Raters positioned the scale on the lateral aspect of the patient's eye, moving it to locate the circle on the scale corresponding to the pupil's size. Raters completed a form recording each pupil size and whether there was anisocoria.

Interrater (e.g., assessing Rater 1 versus Rater 2) and intrarater (assessing the same rater's ratings over Trials 1 and 2) reliability were measured with the intraclass correlation coefficient (ICC).⁵ Kappa measures were used to evaluate differences in raters' assessment of anisocoria. To determine if there were differences between the raters' objective and subjective assessments, a two-factor ANOVA—using as factors raters,^{1,4} pupil side (right [RP]/left [LP]), and trial (I/II)—was performed.

Results. Using an objective scale, the raters reported larger median pupil sizes. At the first trial, the interrater reliability for the whole group was fair (ICC, 0.40 LP) to moderate (0.43 RP). Raters using the scale achieved substantial agreement, whereas those using their own impression had moderate agreement (table). There were significant differences between Raters 3 and 4, and between them and those using the scale. No differences were found between Raters 1 and 2.

At the second trial, the whole group achieved similar interrater reliability (0.47). Likewise, interrater agreement for raters who used the scale was better than for those using their impression (see the table).

Intrarater reliability was substantial to optimal (see the table). A two-factor ANOVA showed differences in pupil measurements between raters ($p < 0.0001$) but not between trials. Differences were between Raters 3 and 4 ($p < 0.0002$), and between them and Raters 1 and 2 ($p < 0.0001$), but not between Raters 1 and 2. There was no interaction between raters and trials.

Anisocoria. Interrater reliability of the four raters was slight (0.18). Interrater reliability between raters using objective and subjective measures was also slight. There were no significant differences between trials. Raters using the scale reported anisocoria more often (23 versus 9 of 100 subjects).

Table Inter- and intrarater reliability

Raters	Right pupil (n = 100)	Left pupil (n = 100)
Interrater		
1 vs 2 (Trial I)	0.68	0.63
3 vs 4 (Trial I)	0.49	0.47
1 vs 2 (Trial II)	0.79	0.77
3 vs 4 (Trial II)	0.50	0.50
Intrarater		
1	0.62	0.54
2	0.87	0.85
3	0.67	0.68
4	0.80	0.76

Data presented as intraclass correlation coefficient. Raters 1 and 2 used scales; Raters 3 and 4 used their impression.

Discussion. Our study demonstrates that physicians using a scale achieved consistently better interrater reliability (substantial) than those using their own impression (moderate). This finding is particularly relevant when patients are assessed by different physicians in potentially evolving emergency situations. However, the method of assessment did not influence the intrarater reliability.

In the current study, each neurologist independently assessed a large number of subjects randomly assigned to assure sufficient statistical power. Our study design eliminated methodologic bias related to order of evaluation and lack of blindness, which limited the interpretation of previous studies.^{3,4}

Our study, similar to previous ones,^{6,7} showed a low interrater reliability of neurologists in assessing anisocoria. This finding should be carefully interpreted because kappa is a measure that considers agreement beyond chance. The study group consisted of 100 normal subjects, most without anisocoria, and when the number of events is low, the chance of agreement increases. In fact, raters' percentage of agreement (91%) and agreement by chance were high (87%). It could be argued that the lack of an a priori definition of anisocoria contributes to a low interrater agreement.

Based on our findings, a graded scale should be used when more than one physician assesses pupillary diameter. However, when the same physician evaluates the pupils, the subjective method may still be reliable, if one excludes potential emergency evolving neurologic situations. Whether an a priori working definition of anisocoria will improve interrater reliability needs to be determined.

Key words: Reliability—Pupil assessment.

From the Neuropharmacology Unit (Dr. Litvan), Defense and Veteran Head Injury Program, Henry M. Jackson Foundation and Medical Neurology Branch, NINDS, NIH, Bethesda, MD; Departamento de Neurologia (Drs. Saposnik, Mauriño, Gonzalez, Saizar, and Sica), Hospital Ramos Mejia, Buenos Aires, Argentina; and Dr. Bartko, statistical consultant, Bethesda, MD.

Received July 20, 1999. Accepted in final form September 6, 1999.

Address correspondence and reprint requests to Dr. Irene Litvan, Cognitive Neuropharmacology Unit, Defense and Veteran Head Injury Program, Henry M. Jackson Foundation, The Chaplain Building, Suite 600, 6410 Rockledge Dr., Bethesda, MD 20814-1844.

Copyright © 2000 by the American Academy of Neurology

References

- DeJong RN, Haerer AF. Case taking and the neurologic examination. In: Joynt R, ed. Clinical neurology. Vol. I. Philadelphia: JB Lippincott, 1995: 49–68.
- Bradley WG, Daroff RB, Fenichel GM, Marsden CD. Neurology in clinical practice. Principles of diagnosis and management. 2nd ed. Boston: Butterworth-Heinemann, 1996:209–218.
- Lord-Feroli K, Maguire-McGinty M. Toward a more objective approach to pupil assessment. *J Neurosurg Nurs* 1985;17:309–312.
- Wilson S, Amling JK, Floyd SD, McNair ND. Determining interrater

reliability of nurses' assessment of pupil size. *J Neurosci Nurs* 1988;20: 189–192.

- Bartko JJ, Carpenter WT. On the methods and theory of reliability. *J Nerv Ment Dis* 1976;163:307–317.
- Hansen M, Christensen PB, Sindrup SH, Olsen NK, Kristensen O, Friis ML. Inter-rater variation in the evaluation of neurological signs. *J Neurol* 1994;241:495–504.
- Vogel HP. Influence of additional information on the interrater reliability in the neurologic examination. *Neurology* 1992;42:2076–2081.

A clinical examination technique for mild upper motor neuron paresis of the arm

Donald F. Weaver, MD, PhD, FRCPC

Recognizing subtle upper motor neuron arm paresis is fundamental to the neurologic examination.¹ Although the pronator drift test is widely used, others have contributed observations: Souque (see reference 2) described abduction of all fingers in the outstretched paretic hand; Wartenberg³ observed finger spreading in a single patient asked to press down with his paretic hand; Alter⁴ described the *digiti quinti* sign (isolated little finger abduction with outstretched hands, palms downward). Although these signs are useful, there are inconsistencies concerning their elicitation and utility.

To achieve a rigorous examination technique, 50 consecutive patients (“training set”) with mild unilateral arm weakness were prospectively evaluated by the author. Mild weakness was defined as minimal reduction in strength inapparent to the patient's family and coworkers but manifesting as subtle difficulty in routine activities. Patients were excluded if they had weakness from a peripheral nerve lesion and were included only after imaging demonstrated an appropriate CNS lesion. Of these 50 patients, four had no arm weakness on clinical examination—two of these had ipsilateral nasolabial fold flattening, and two had no signs. Thirty-eight had a positive pronator drift: 1) 35/38 showed concomitant mild detectable weakness with resistive strength testing, 3/38 had no weakness with resistive strength testing; 2) 34/38 showed pronator drift when the fingers were either together or apart, 4/38 showed drift only when the fingers were spread apart; 3) 28/38 showed a downward shift of the hand, 10/38 showed only slow wrist pronation. Eight patients had no pronator drift, but did demonstrate finger spreading: four showed spreading of all fingers, and four showed only little finger abduction. Of the four patients with little finger abduction, this occurred in all four with palms upward and in two with palms downward. Of the 38 with pronator drift, they all did so within 30 seconds (24/38 by 15 seconds; 33/38 by 20 seconds). In those with finger spreading, this always occurred within 13 seconds. The four patients with no signs did not develop pronator drift even after 60 seconds. Eight patients had obvious arm weakness rendering pronator drift or resistive strength testing unnecessary for arm weakness detection.

Based on these data, the following examination technique was devised. With eyes closed (precluding visual compensation), the patient (seated or standing) holds both arms outstretched in front; the elbows and wrists are extended, and the hands are open with the palms supinated and pointed upward. Initially, the patient is asked to keep his or her fingers together for 15 seconds. Next, the patient spreads the fingers apart and is observed for an additional 15 seconds. Thus, the technique has two equal observation phases: fingers together (Phase I) and fingers apart (Phase II). During Phase I, there are two indicators of upper motor neuron weakness: a) little finger abduction or b) finger spreading. During Phase II, there are two indicators: a) slow wrist pronation with slight elbow flexion or b) downward and lateral drift of the hand. Phase II indicators may occur during Phase I observation.

This technique was validated by being applied to the next 25 consecutive patients (“test set”) presenting with the same inclusion/exclusion criteria. Three subjects had little finger abduction (Ia), one had finger spreading (Ib), six had hand pronation (IIa), and 14 had arm drift (IIb). One had no signs.

During Phase I, little finger abduction was better seen when the outstretched hands were palms up (opposite to the *quinti digiti* sign). During Phase II, there was improved drift elicitation when the fingers were spread, rather than together. Pronator drift always occurred within 30 seconds and did not require a full minute.⁵ This overall examination technique does not support the

notion that little finger abduction → finger spreading → hand pronation → arm drifting is an observable continuum.

Care must be taken to avoid false positives: with ulnar nerve injury, little finger abduction may occur; in cerebellar disease, an outstretched arm may drift downward and outward; in proprioceptive disorders, an outstretched arm may elevate. A control group of 50 patients (mean age 68 years) with no arm weakness complaints and with no imaging abnormalities was evaluated: 49/50 had no pronator drift, 1/50 had little finger abduction.

This method of developing a clinical examination technique using a training set and a test set for prospective validation is unique; signs are normally described in a small group of patients on a retrospective ad hoc basis. Modifying the time-honored neurologic examination for improved reliability and quantifiability is not commonly pursued. However, the use of therapeutics whose administration is influenced by the presence of neurologic signs may render this a necessary pursuit.

Key words: Upper motor neuron paresis—Clinical examination—Examination technique.

From the Departments of Medicine and Chemistry, Queen's University, Ontario, Canada.

Received April 28, 1999. Accepted in final form September 11, 1999.

Address correspondence and reprint requests to Dr. Donald F. Weaver, Departments of Medicine and Chemistry, Queen's University, Kingston, Ontario, Canada, K7L 3N6.

Copyright © 2000 by the American Academy of Neurology

References

1. DeJong RN. The neurologic examination. New York: Harper & Row, 1979:453–455.
2. Monrad-Krohn GH, Refsum S. The clinical examination of the nervous system. New York: Harper & Row, 1964:145.
3. Wartenberg R. The examination of reflexes, a simplification. Chicago: Year Book Medical Publishers, 1945:178.
4. Alter M. The digiti quinti sign of mild hemiparesis. *Neurology* 1973;23:503–505.
5. Lindsay KW, Bone I, Callander R. Neurology and neurosurgery illustrated. New York: Churchill-Livingston, 1991:19.

Superior sagittal sinus thrombosis due to lithium: Local urokinase thrombolysis treatment

M. Wasay, MD; R. Bakshi, MD; S. Kojan, MD; G. Bobustuc, MD; and N. Dubey, MD

Superior sagittal sinus thrombosis (SSST) is associated with a host of predisposing factors, including pregnancy, collagen vaso-

lar disease, malignancy, diabetes insipidus, and medications such as oral contraceptive agents, L-asparaginase, androgens, and heparin.¹ The diagnosis of cerebral venous thrombosis may be challenging,² so it is important to recognize underlying causes. We report a young woman with SSST associated with lithium-induced nephrogenic diabetes insipidus. This is the first reported case of venous sinus thrombosis secondary to lithium therapy. The patient was treated successfully with local urokinase thrombolysis.

Case report. A 30-year-old woman with a history of bipolar disorder presented with progressive headache, confusion, visual blurring, and left hemiparesis. She had been taking lithium, risperidone, and oral contraceptive agents for many years. Neurologic examination showed confusion, papilledema, and mild left hemiparesis. Urine output was markedly elevated (greater than 200 mL/hour). Significant laboratory abnormalities included serum platelet count 106,000/mm³, sodium 154 mEq/L, serum osmolality 305, urine sodium 43 mEq/L, and urine osmolality 165. A desmopressin challenge test was consistent with nephrogenic diabetes insipidus. The patient was diagnosed with lithium-induced diabetes insipidus and lithium was discontinued. Noncontrast head CT scan demonstrated hyperdensities involving the superior sagittal sinus (SSS), straight sinus (SS), and vein of Galen (figure, A). Cerebral angiogram showed thrombosis of SSS, SS, left transverse sinus, and left sigmoid sinus (figure, B). After femoral vein entry, a Tracker-18 (Target Therapeutics, Freemont, CA) catheter was advanced coaxially over a guide wire and introduced into the SS and a bolus of 250,000 units of urokinase was given followed by continuous infusion at 80,000 units/hour. The catheter was forwarded and placed into the SSS and urokinase infusion at 80,000 units/hour was continued into the SSS for 3 days. Patency of the SSS and SS was identified on a repeat angiogram (see figure, C). The patient was then given systemic heparinization followed by oral warfarin. The patient's neurologic status improved to normal by the time of discharge. An extensive laboratory evaluation for hypercoagulable states was negative. The patient was not rechallenged with lithium or oral contraceptive agents.

Discussion. Lithium, a commonly used medication for the treatment of bipolar disorder, is known to cause nephrogenic diabetes insipidus.³ The mechanism underlying lithium-induced nephrogenic diabetes insipidus is impairment of vasopressin-sensitive adenylate cyclase activity causing failure of water reabsorption in the distal renal tubules. Additionally, lithium may cause decreased water intake due to impairment of thirst sensation, contributing to dehydration. Thus, lithium can cause dehydration by several mechanisms, and this dehydration is an important risk factor for SSST.¹ To our knowledge, this is the first reported case of venous sinus thrombosis secondary to nephrogenic diabetes insipidus. Similar to our case, lithium-related nephrogenic diabetes insipidus usually resolves after discontinuation of lithium.³ In addition to lithium, our patient was taking oral

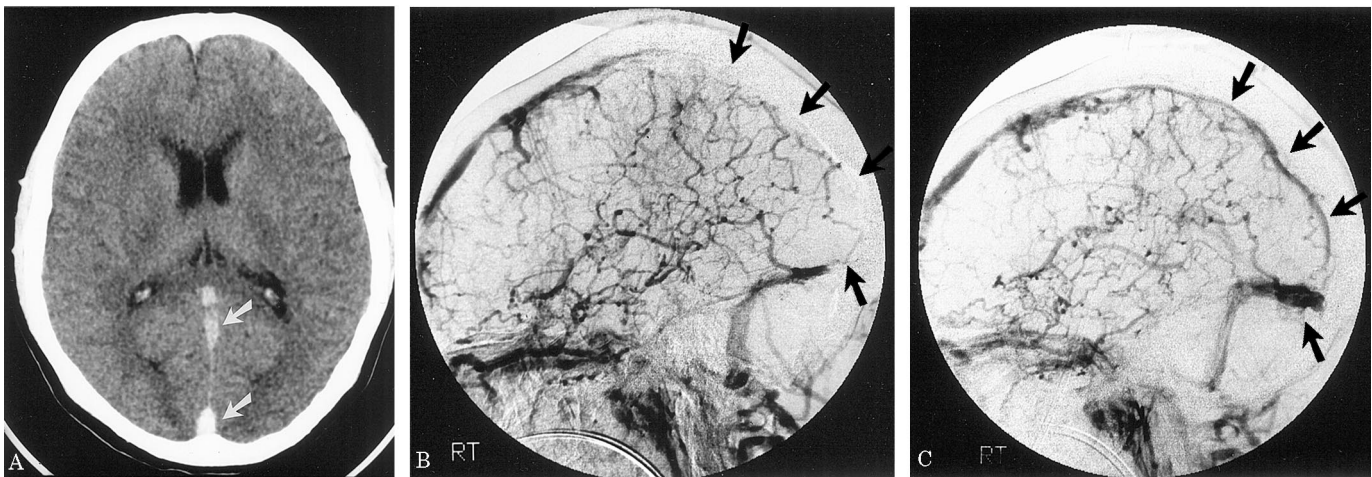


Figure. (A) Noncontrast axial head CT scan through the level of the midthalamus shows increased densities (arrows) in the vein of Galen, straight sinus, and superior sagittal sinus, consistent with thrombosis. (B) Cerebral angiogram (lateral projection) shows thrombosis of the superior sagittal sinus and the straight sinus before treatment (arrows). (C) 70 hours after direct urokinase thrombolysis, recanalization is noted (arrows).

contraceptives, which may have been an additional risk factor for SSST.² Oral contraceptive agents are known to cause a significant rise in serum profibrinolysin and fibrinogen, leading to a decrease in spontaneous fibrinolytic activity.⁴

SSST may be associated with a high morbidity if untreated.¹ Selective catheterization of dural venous sinuses and direct thrombolysis with local urokinase infusion may be safe and effective for SSST. Since 1991, more than 40 cases of venous sinus thrombosis treated with local urokinase have been reported.⁵⁻⁶ Our case is in agreement with these previous observations that direct thrombolysis is safe and effective for dural venous thrombosis. IV heparin anticoagulation is recommended as the standard therapy for SSST.¹ A retrospective study by the current authors comparing local urokinase thrombolysis to heparin therapy for SSST suggests that thrombolysis treatment is associated with better neurologic recovery.⁷ Thus, a randomized, prospective trial comparing urokinase thrombolysis with heparin anticoagulation is warranted.

Patients presenting with diabetes insipidus and acute neurologic dysfunction should be evaluated for venous sinus thrombosis. A combination of oral contraceptive agents and lithium should be used with caution. Furthermore, in patients with diabetes insipidus, underlying causes should be identified and dehydration should be treated aggressively to reduce the risk of developing SSST.

Key words: Superior sagittal sinus thrombosis—Lithium—Urokinase treatment.

From Imaging Services (Drs. Wasay, Bakshi, and Dubey), Kaleida Health—Millard Fillmore Hospital, Buffalo, NY; the Department of Neurology (Dr. Bakshi), State University of New York at Buffalo; the Department of Neurology (Dr. Kojan), University of Texas Southwestern Medical Center, Dallas; and the Department of Neurology (Dr. Bobustuc), University of Texas, Houston.

Presented in preliminary form at the 1999 annual meeting of the American Society of Neuroimaging; Scottsdale, AZ; February 25, 1999.

Received March 3, 1999. Accepted in final form September 16, 1999.

Address correspondence and reprint requests to Dr. Rohit Bakshi, Neuroscience Center, E-2, Buffalo General Hospital, 100 High Street, Buffalo, NY 14203.

Copyright © 2000 by the American Academy of Neurology

References

1. Ameri A, Bousser MG. Cerebral venous thrombosis. *Neurol Clin* 1992;10:87-111.
2. Bakshi R, Lindsay BD, Bates VE, Kinkel PR, Mechtler LL, Kinkel WR. Cerebral venous infarctions presenting as enhancing space-occupying lesions: MRI findings. *J Neuroimaging* 1998;8:210-215.
3. Ramsey TA, Cox M. Lithium and the kidney: a review. *Am J Psychiatry* 1982;139:443-449.
4. Phillips LL, Turksoy RH, Southam AL. Influence of ovarian function on

fibrinolytic system. II. Influence of exogenous steroids. *Am J Obstet Gynecol* 1961;82:1216-1220.

5. Horowitz M, Purdy P, Unwin HD, et al. Treatment of dural sinus thrombosis using selective catheterization and urokinase. *Ann Neurol* 1995;38:58-67.
6. Kasner SE, Gurian JH, Grotta JC. Urokinase treatment of sagittal sinus thrombosis with venous hemorrhagic infarction. *J Stroke Cerebrovasc Dis* 1998;7:421-425.
7. Wasay M, Bakshi R, Kojan S, et al. Local urokinase thrombolysis versus systemic heparin anticoagulation treatment of sagittal sinus thrombosis: analysis of 40 patients. *Neurology* 1999;52(suppl 2):A63. Abstract.

Paroxysmal word deafness secondary to focal epilepsy

Victor S.C. Fung, MB, BS; Carolyn M. Sue, PhD; and Ernest R. Somerville, MB, BS

Word deafness is characterized by a deficit in auditory verbal comprehension, repetition, and writing to dictation with relative preservation of other language functions.^{1,2} It can follow bilateral^{1,2} or unilateral^{3,4} lesions of the temporal lobes. We report a patient who developed paroxysmal episodes of word deafness with normal auditory comprehension between attacks. Electroencephalographic (EEG) monitoring showed that word deafness was an ictal manifestation of focal epilepsy.

Case report. A 48-year-old right-handed man had a 2-day history of paroxysmal deafness. At the onset of each episode he heard muffled voices in both ears followed within seconds by loss of hearing. Each attack resolved spontaneously over 3 to 5 minutes. The attacks occurred up to every 10 minutes. There were no accompanying symptoms. Seven years earlier, he had a right middle cerebral artery territory infarct resulting in a mild left hemiparesis and secondarily generalized seizures with focal motor onset, treated with carbamazepine.

The patient was examined during several paroxysmal episodes. He signaled the onset of each turn by exclaiming "It's happening. I'm going deaf. I can hear voices . . . I can't hear what they're saying." Seconds later, he would say: "I'm deaf . . . I can't hear you." In response to verbal commands with the examiner facing him, he stated he was deaf. He did not respond when the examiner was out of view. Spontaneous speech was normal but limited in content. He obeyed simple written three-step commands and could read aloud and copy simple sentences. Nonverbal auditory comprehension was tested with the examiner behind the patient. He identified barking as a dog and bleating as a sheep, but mistook meowing for a horse. He was able to identify and count claps.

Language function was normal interictally, but he had deficits in verbal and nonverbal memory on psychometric testing. He had a mild left hemiparesis and sensory inattention.

Interictal EEG showed focal slowing over the right temporal region. At the onset of each turn, EEG seizure activity developed over the left hemisphere, which phase reversed in the centropari-

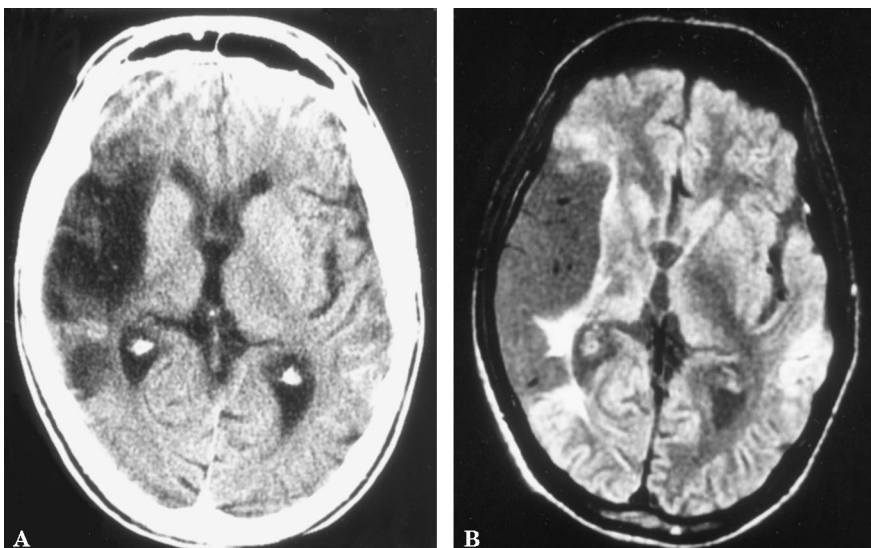


Figure. Cerebral CT on day 2 (A) and MRI on day 7 (B) show an old right temporoparietal infarct and a stippled area of high signal intensity in the left midtemporal cortex consistent with recent hemorrhagic infarction.

etal region and lasted approximately 90 seconds. Impaired auditory verbal comprehension persisted up to 150 seconds longer.

Neuroimaging showed an old right temporoparietal infarct and a recent hemorrhagic infarct in the left midtemporal cortex (figure). Pure tone audiometry showed mild sensorineural hearing loss. Brainstem auditory evoked responses were normal.

No further episodes of paroxysmal deafness occurred after his carbamazepine dose was increased.

Discussion. Our patient presented with paroxysmal deafness as the predominant symptom, and examination during attacks revealed a total deficit in verbal auditory comprehension. Nonverbal auditory comprehension was relatively spared as indicated by the ability to recognize animal noises and clapping, and there was also relative preservation of nonauditory language processes. Although his deficits were not strictly confined to word deafness, this finding dominated the clinical syndrome. It is recognized that many patients categorized as having "pure" word deafness also have mild-to-moderate deficits in other language modalities or nonverbal auditory comprehension.^{1,5}

The temporal relationship of clinical symptoms, neurologic deficit and EEG seizure activity, and remission of attacks following increase in anticonvulsant therapy provides strong evidence that paroxysmal word deafness was a manifestation of focal epilepsy. Word deafness always developed within seconds of the onset of EEG seizures, suggesting that it was an ictal phenomenon. Word deafness also remained for up to 150 seconds following resolution of seizure activity detected on surface EEG, suggesting that the neurologic deficit may have been partly postictal.

Patients with word deafness may complain of deafness, incomprehensible background voices, or an unpleasant background noise.⁵ It has been suggested that auditory hallucinations occurring in the setting of word deafness are analogous to visual hallucinations in Anton's syndrome.¹ Our patient was able to hear incomprehensible distant voices at the onset of his EEG seizures, providing evidence that such hallucinations may be an epileptic phenomenon.

It is of interest that although the old right temporoparietal

infarct was extensive and probably involved primary auditory cortex, the left-sided infarct probably did not destroy primary auditory cortex, and thus in itself did not disrupt language function. Its role in the pathogenesis of word deafness was as an epileptogenic lesion. It was the area of nonfunctioning cortex in the left hemisphere produced by the seizure, either alone or in combination with the contralateral lesion, that caused word deafness. The unusual combination of these two different sized lesions presumably accounts for why paroxysmal word deafness is such a rare phenomenon.

We suggest that word deafness can be a reversible disorder due to focal epilepsy. An EEG should be performed in patients presenting with word deafness, especially if it is paroxysmal, to exclude this treatable cause.

Key words: Word deafness—Seizures—Epilepsy—Temporal lobes—Stroke.

From the Comprehensive Epilepsy Unit, Department of Neurology, Westmead Hospital, Sydney, Australia.

Received June 15, 1999. Accepted in final form September 22, 1999.

Address correspondence and reprint requests to Dr. Victor Fung, Department of Neurology, Westmead Hospital, Westmead NSW 2145, Australia.

Copyright © 2000 by the American Academy of Neurology

References

1. Buchman AS, Garron DC, Trost-Cardamone JE, Wichter MD, Schwartz M. Word deafness: one hundred years later. *J Neurol Neurosurg Psychiatry* 1986;49:489–499.
2. Coslett HB, Brashear HR, Heilman KM. Pure word deafness after bilateral primary cortex infarcts. *Neurology* 1984;34:347–352.
3. Geschwind N. Disconnexion syndromes in animal and man. Parts I and II. *Brain* 1965;88:237–294, 585–644.
4. Roberts M, Sandercock P, Ghadiali E. Pure word deafness and unilateral right temporoparietal lesion: a case report. *J Neurol Neurosurg Psychiatry* 1987;50:1708–1709.
5. Mendez MF, Geehan GR. Cortical auditory disorders: clinical and psychoacoustic features. *J Neurol Neurosurg Psychiatry* 1988;51:1–9.

Neurology[®]

Paroxysmal word deafness secondary to focal epilepsy
Victor S. C. Fung, Carolyn M. Sue and Ernest R. Somerville
Neurology 2000;54;533
DOI 10.1212/WNL.54.2.533

This information is current as of January 25, 2000

Updated Information & Services	including high resolution figures, can be found at: http://www.neurology.org/content/54/2/533.full.html
References	This article cites 5 articles, 5 of which you can access for free at: http://www.neurology.org/content/54/2/533.full.html#ref-list-1
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.neurology.org/misc/about.xhtml#permissions
Reprints	Information about ordering reprints can be found online: http://www.neurology.org/misc/addir.xhtml#reprintsus

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright . All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.

