Chorea-Acanthocytosis: Report of a Family and Neuropathological Study of Two Cases

Ma. Elisa Alonso, Fernanda Teixeira, Guillermo Jimenez and Alfonso Escobar

ABSTRACT: We report three siblings, offspring of normal consanguineous parents, with a progressive neurological illness that began in midlife and was characterized primarily by chorea and leading to death in the fourth decade. The proband had erythrocyte acanthocytosis with normal serum β-lipoprotein. Biopsy of left gastrocnemius muscle showed neurogenic muscular atrophy. There was a decrease in the numbers of large myelinated axons of the sural nerve. Postmortem examination of two cases showed marked atrophy, neuronal loss and gliosis of the caudate nucleus and putamen. Autosomal recessive inheritance is likely in this family.

RÉSUMÉ: *Chorée avec acanthocytose: compte rendu d'une famille et étude neuropathologique de deux cas* Nous rapportons le cas de trois membres d'une même famille atteints d'une maladie neurologique progressive ayant débutée à l'âge moyen et caractérisée essentiellement par de la chorée avec décès dans la trentaine. Ils étaient issus de parents normaux mais consanguins. Le cas index avait une acanthocytose érythrocytaire avec une ß-lipoprotéine sérique normale. Une biopsie des muscles jumeaux de la jambe gauche a montré une atrophie musculaire neurogénique. Il y avait une diminution du nombre des gros axones myélinisés au niveau de nerf surai. Une autopsie pratiquée sur deux cas a montré une atrophie importante ainsi qu'une perte neuronale et une gliose du noyau caudé et du putamen. Il s'agit vraisemblablement d'une maladie dont l'hérédité est autosomale dominante dans cette famille.

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Abnormal erythrocytes characterized by spiny superficial projections are known as acanthocytes. These cells led to the initial differentiation of the abetalipoproteinemia or Bassen-Kornzweig disease from other forms of retinitis pigmentosa. Acanthocytes, although not unique to abetalipoproteinemia, are seen as a signal reflection of the effects of the plasma lipoprotein abnormality on plasma membrane structure and function.[1]

In 1967, Estes et al[2] reported a new hereditary acanthocytosis syndrome that consists of mental changes, choreic involuntary movements, limb muscular atrophy and acanthocytosis, without serum lipoprotein deficiency.[3] Neuropathological studies revealed severe degeneration of the basal ganglia and denervation atrophy of muscle.[4]

This progressive illness develops in midlife and has almost always an autosomal recessive inheritance pattern.

This report describes a family with likely autosomal recessive inheritance with four affected individuals, two of whom were studied post-mortem.

Case Reports

Case 1

The proband (V-8, Figure 1) was a 38-year-old man, married, engineer by profession, who was well until age 33, when he noticed the insidious onset of progressive choreiform movements, difficulty in swallowing and slurred speech. By age 35 he could not work anymore because of the severity of his symptoms; however, the relatives who lived with him denied any signs of mental deterioration. At age 39, he was admitted to the National Institute of Neurology and Neurosurgery, in Mexico City. He was alert, oriented and cooperative. Results of cardiac, pulmonary and abdominal examinations were normal. He had intermittent involuntary oral, facial and limb movements, that provoked difficulty to vocalize and swallow. Neurological examination disclosed generalized hypotonia and hyporeflexia, orofacial movements, dysarthria and dysphagia. The remaining cranial nerves were normal as were all moralities of sensation. The family pedigree is shown in Figure 1.

Laboratory data: Urinalysis, blood cell count, glycemia, glutamic pyruvic and glutamic oxalacetic transaminase activities and serum levels of cholesterol, triglycerides and fractionated lipoproteins were all within normal limits. The cerebrospinal fluid sample was normal.

From the Department of Genetics (M.E.A.), Department of Experimental Neuropathology (F.T.), Department of Pathology (A.E.), National Institute of Neurology and Neurosurgery of Neurobiology Istituto de Investigaciones Biomédica, México, D.F.

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Reprint requests to: M.E. Alonso, Department of Genetics, Research Division, National Institute of Neurology and Neurosurgery, Insurgentes Sur 3877 C.P. 14410, México, D.F.

Creatine phosphokinase activity could not be assayed. More than 20% of the red blood cells seen in wet preparations examined by phase contrast and in dry films stained by Wright technique were acanthocytes (Figure 2).

Nerve conduction velocities, measured at a limb surface temperature of 32°C to 35°C, were as follows (normal in parentheses): left cubital (elbow-wrist): 45 m/s (60 ± 4); right posterior tibial (knee-ankle): 47 m/s; left posterior tibial: 41 m/s (54.9 ± 7.6); right popliteal sciatic (knee-ankle): 44 m/s; left popliteal sciatic: 31 m/s (56.2 ± 4.3).

Computerized tomographic scanning revealed widening of the frontal horns of lateral ventricles.

In the Wechsler adult intelligence scale, his verbal intelligence quotient was 91, and the performance could not be assessed. Muscle and nerve biopsies were obtained.

The patient improved of his movements with haloperidol and chlorpromazine and was discharged. Three months later, he returned to the Institute with the same neurological picture, plus an associated bacterial infection, manifested by fever, dysuria and abdominal pain. He developed septicaemia and died three days later.

Nerve biopsy After local anesthesia, a full-thickness, 1-cm long segment of the left sural nerve was removed, fixed in buffered 1% osmium tetroxide and embedded in paraffin wax.

Transverse 5 micron-thick sections were photographed and printed with a final magnification of 1,200 times. Numbers of myelinated axons were recorded and the figures per square millimeter were calculated by extrapolation. The external diameters (including myelin sheath thickness) were measured with a Zidas image analyser (Carl Zeiss Inc.) and frequency histograms were prepared. The sural nerve obtained at post-mortem from an individual of the same sex and age without neurological abnormalities, was used as control (Figure 3a).

Microscopical examination showed an apparent decrease in the number of large myelinated fibres (Figure 3b), that was confirmed with quantitative studies. The numbers of such fibres per millimeter squared was 4,372 in the present case, and 9,644 for the control. The frequency histogram (Figure 4), is abnormally unimodal, with a peak in the 3- to 5-micrometer range. There is a deviation to the left, with marked decrease in the number of fibres above 10 micrometers in diameter.

Muscle biopsy findings The biopsy of the left gastrocnemius muscle (Figure 5a and b) showed variation of fibre size, with occasional small angulated fibres and an excess of fibres in the 20- 40-micrometer range. The variability coefficient (standard deviation × 1000 divided by mean) was 361.3 (upper normal limit: 250).[5] The atrophy factor[6] was 607 (normal for sex and muscle: 150). There were occasional necrotic fibres (Figure 5b, arrows) and internal nuclei were present in 9% of the cells (Figure 5a, arrows). The histogram (Figure 6) was bimodal, with peaks at the 30- and 60-micrometer marks.

Autopsy neuropathological findings The weight of the brain was 1,407 g. Coronal sections depicted bilateral atrophy of the head of the caudate nuclei associated with widening of the frontal horn of the lateral ventricles (Figure 7). The globus pallidus appeared diminished in size and of brownish-gray tint. The remaining structures were within normal limits.

Microscopic findings Sections were embedded in paraffin wax and stained with hematoxylin and eosin, and by the Klüver-Barrera and Masson trichrome techniques. There was a marked reduction in neuron density in both caudate and putamen nuclei, mainly involving small neurons, although few large neurons could be seen. A secondary astrocytic gliosis was present. The myelin stain showed loss of myelinated fibres crossing the corpora striata (Figure 8).

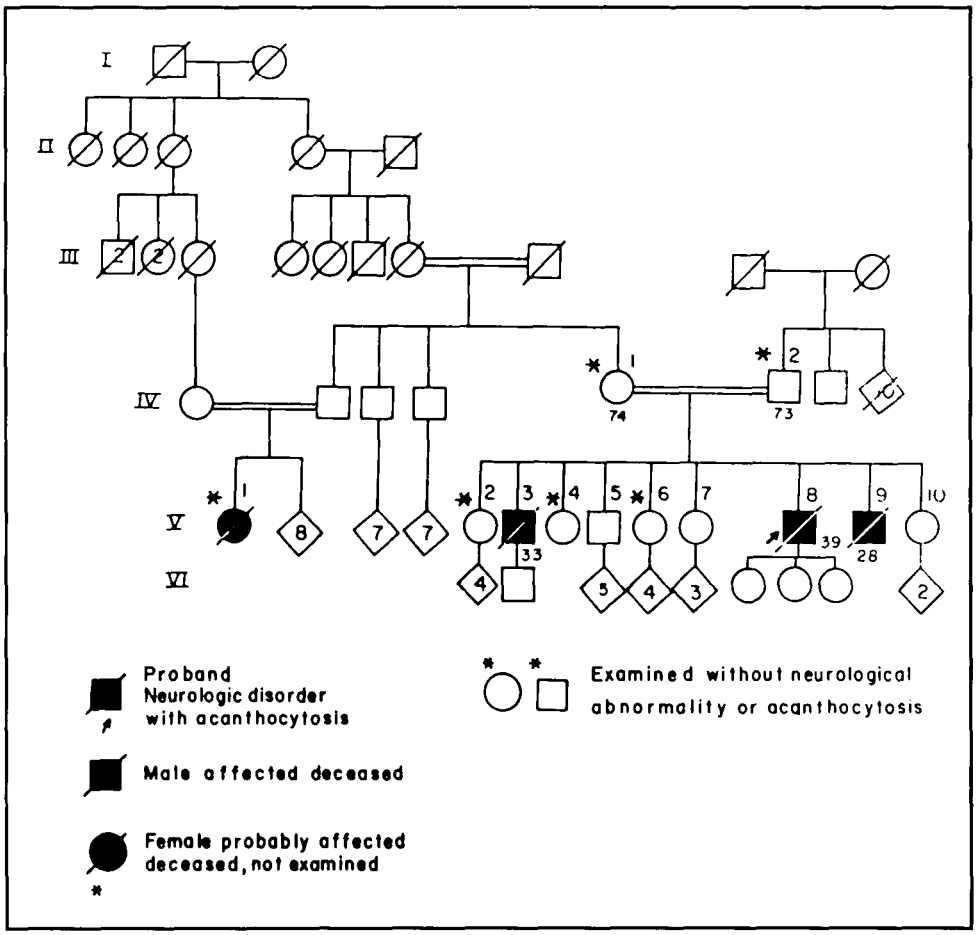

Figure 1 — Pedigree Chart of the family studied.

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Case 2

(Brother of case 1, V-3). This patient had already died when the diagnosis of the familial disease was done, based on data found in our proband. The following data were taken from his hospital files. This was a 29-year-old countryman that had done poorly at primary school and never learned how to read or write. At age 27 he began to have choreiform movements and speech problems, which had a fast evolution, so that by age 28 he was bedridden. At the time of his admission to the Institute, choreiform movements were observed in the head, neck, trunk and limbs.

There was generalized hypotonia and hyporeflexia, but no pathological reflexes were seen. The hypothenar and thenar eminences and the interoseal spaces showed atrophy. There was bilateral pes cavus. Sensory examination showed no deficits.

Laboratory data Urinalysis, blood cell count, glycemia, protein C and antistreptolysin were all within normal limits.

The cerebrospinal fluid sample was normal. His blood group was B+. Radiographic examination of the chest and skull were normal, as was the electroencephalogram. Pneumoencephalogram showed moderate cerebral atrophy.

After receiving 10 mg of haloperidol per day, he improved and was discharged. A year later, his movements were worse, and he had developed insomnia and irritability. He continuously bit his lower lip involuntarily. The dosage of haloperidol was increased to 50 mg with no improvement. He began to present generalized convulsions and died at age 33. No post-mortem studies were done.

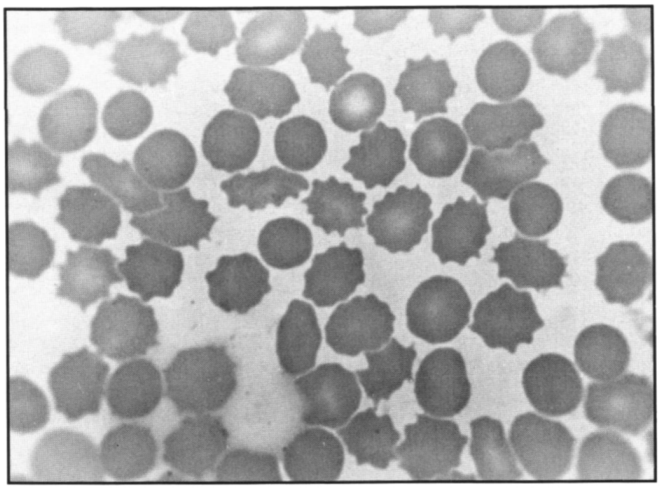

Figure 2 — Peripheral blood smear of the proband patient V-8 showing acanthocytes.

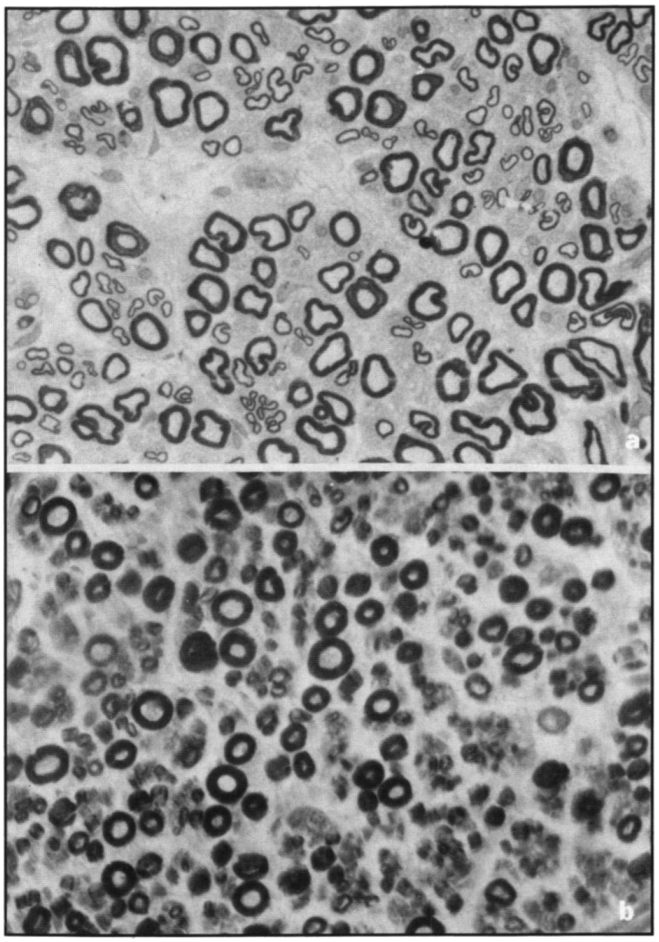

Figure 3A — One micron thick section of normal sural nerve embedded in epoxy resin. Toluidine blue × 500. B — Sural nerve of a case of chorea-acanthocytosis. There is an apparent decrease in the number of larger axons, that was confirmed quantitatively. Paraffin embedded. Os 04 fixed nerve. × 500.

Case 3

(Another proband's brother V-9). As in case 2, the data that follow were taken from his hospital files. This was a 28-year-old single man, with schooling up to the high school level. At age 24 he began to notice irritability and involuntary movements in the face and limbs, associated with weakness in all limbs and difficulty in walking. These symptoms did not progress until three months before his admission, when he developed unmotivated aggressiveness toward his relatives and himself, with suicidal ideas. He consulted a general practitioner, who prescribed a succession of drugs, including haloperidol, chlorpromazine, diazepam and imipramine, which yielded little improvement. One day, he jumped from a second-floor window and was seen to by his family, who brought him to the Casualty Department of the Institute 24 hours later. On admission he was alert, oriented, anxious, with generalized choreiform movements and multiple frayings and wounds on his body hyporeflexia and normal sensibility. He died in the first 24 hours after admission.

Laboratory data Urinalysis, blood cell count and glycemia were normal, as was the sample of cerebrospinal fluid.

An electroencephalogram done after admission was also normal.

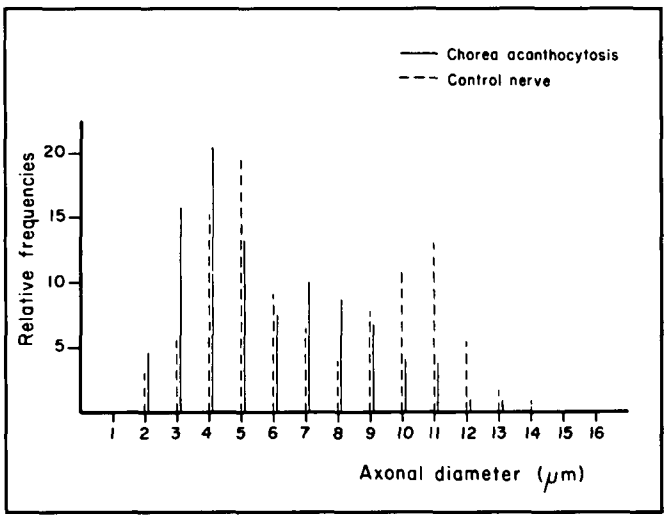

Figure 4 — Histograms showing frequencies of myelinated axons diameters.

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Neuropathologic findings The brain appeared with diffuse leptomenigeal vascular congestion and flattening of the convolutions. Brain weight was 1647 g. An epidermoid cyst was lodged at the base of the brain, extending from the optochiasmatic region to the ventral aspect of the caudal brain stem. It measured 8 × 8 × 3 cm and was of soft, cereous consistency. On sagittal section the third ventricle was displaced upwards and the III cranial nerve compressed by the tumor. Histologically, the walls of the cyst was compound of a thin connective capsule upon which there was stratified squamous epithelium; the contents consisted of layered, homogeneous eosinophilic material. Coronal sections demonstrated moderate atrophy of anterior nuclei and centromedian nucleus of the thalamus. There was some pallor of the locus niger.

Microscopic examination confirmed the great loss of neurons in corpora striata and globus pallidus mainly the pervicellular component. Secondary astrocytic gliosis was evident. The thalamus showed mild gliosis. The cortex was edematous.

Family Investigation

We examined the proband's parents (IV-1 and -2) of 74 and 73 years of age, respectively, as well as three sibs (V-2 of 48 years, V-4 of 42 years and V-6 of 40 years of age) (Figure 1). All were normal neurologically. A blood sample was obtained from all of them to look for acanthocytes, but every one was normal. A sister (V-10) was mentioned, that had slight involuntary movements, but she was not available for examination. A maternal cousin (V-1) had died with a picture similar to that of the proband's. The proband's parents were consanguineous, but they did not know the degree of consanguinity. The cousin's parents were also consanguineous, as shown in the pedigree.

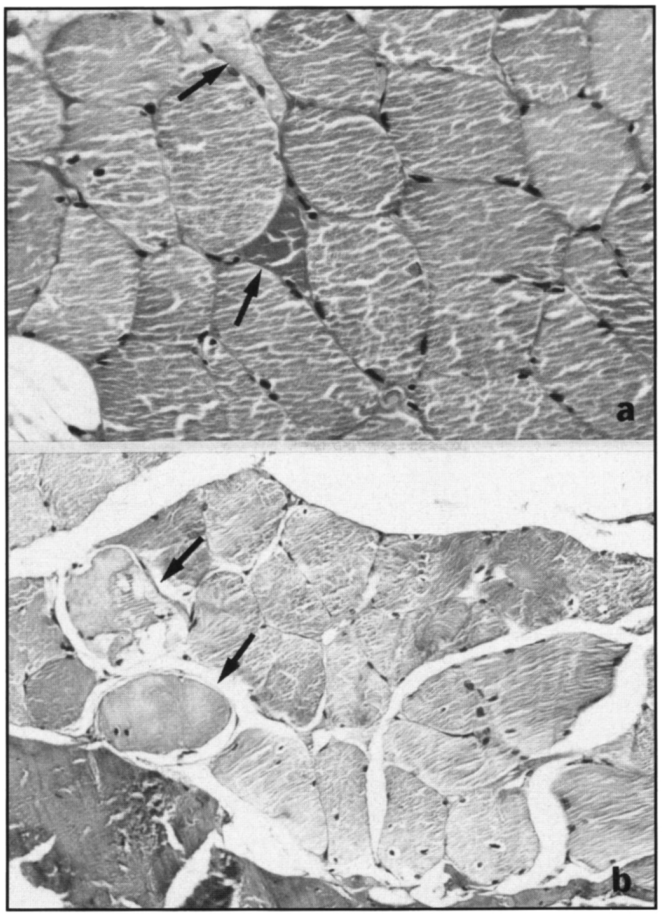

Figure 5A — There is variation of fibre diameter, with small angulated fibres (arrow). Hematoxylin and eosin × 280. B — There was an increased number of fibres with central nuclei, and occasional necrotic fibres (arrows). Hematoxylin and eosin × 200.

Discussion

Our proband had the typical findings of chorea-acanthocytosis, viz adult onset of symptoms, progressive orofacial dyskinesia, choreic movements of the extremities, peripheral neuropathy with muscle denervation, erythrocyte acanthocytosis and hyporeflexia with normal betalipoproteins. Case 2 had, besides, thenar and hypothenar atrophy and bilateral pes cavus, that are also reported in this disease.[7]

One major entity included in the differential diagnosis is Huntington's disease. Two of our patients (V-3 and V-9) were initially thought to have Huntington's disease; however, until they died, none showed signs of dementia and, their parents of advanced age, were neurologically normal. Because of these data, and the autosomal dominant inheritance pattern of Huntington's chorea, the diagnosis was discarded.

Sakai et al[8] studied the typical findings in chorea-acanthocytosis, namely increased levels of creatine phosphokinase, acanthocytosis and muscle denervation, and concluded that these clinical and laboratory features permit differentiation from Huntington's chorea.

After the initial report by Estes et al,[2] new familial cases were studied by Levine et al,[3] Critchley et al.[9,10] Aminoff[11] and Kito.[7] Bird et al[4] reported an additional family with an autosomal recessive inheritance pattern, and for the first time described the neuropathological and neurochemical findings. The former were identical to those observed in our patients. Enzyme activities of glutamic acid decarboxylase (GAD) and choline acetyltransferase (CAT) were shown to be normal in the cerebral cortex, caudate and putamen, in contrast with tissues from patients with Huntington's chorea, in which GAD, and to a lesser degree, CAT, are decreased.

Ohnishi et al[12] studied biopsies of short peroneal muscles

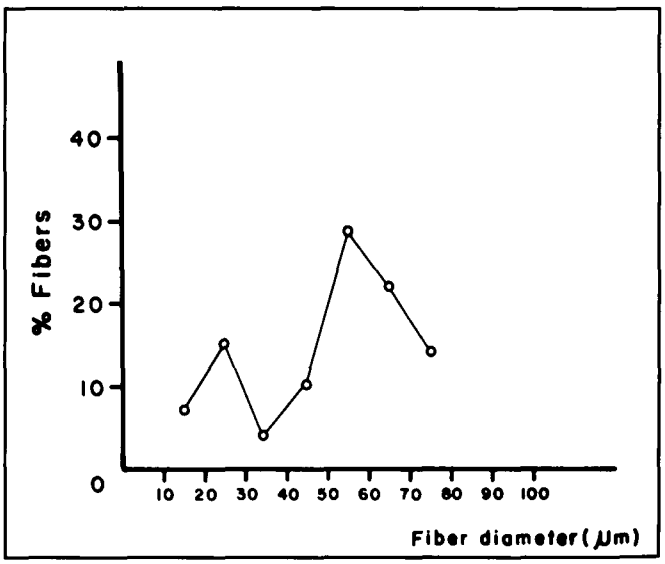

Figure 6 — Frequency histogram of muscle fibre diameters.

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and sural nerves of three cases of chorea acanthocytosis and concluded that neurogenic muscular atrophy should be included as one of the main pathological findings in this disease. In the first case, the presence of small angulated fibres and the shape of the histogram are compatible with denervation atrophy. Although simple necrosis and increased numbers of internal nuclei are usually associated with myopathy, they are occasionally seen in biopsies of denervated muscle, and have also been described in the peroneus muscle of four cases of chorea-acanthocytosis.[13]

The family presented here constitutes an example of autosomal recessive inheritance pattern. There were several consanguineous marriages in the family, as in the case of the proband, whose maternal great-grandmothers were possibly sister or cousins, and that of the affected cousin, who was not examined by us (see Figure 1).

Although all the ancestors remembered by the relatives were Mexicans, the Spanish origin of this family is very likely, for the presence of one subject with blood type B, which is indicative of crossing with foreign blood, mostly, in case of Mexico, with Spanish. Gross[14] also reported a family with chorea-acanthocytosis that had a similar racial ancestry.

In the McLeod blood group phenotype, a presumably defective membrane protein appears to induce a substantial reduction in osmotic water permeability in erythrocytes, which leads to acanthocytosis. Schwartz et al[15] reported the cases of two male patients with McLeod phenotype who had elevated creatine kinase levels, acanthocytosis, normal lipid levels and neurological abnormalities characteristic of chorea-acanthocytosis. Because the patients of Gross's[14] did not have the McLeod phenotype, this does not seem to be a prerequisite to manifest chorea-acanthocytosis. In our cases, the McLeod phenotype was not investigated.

Spitz et al[16] include cases of chorea-acanthocytosis in what they called "neuroacanthocytosis syndrome". Because acanthocytosis can be associated with neurological disorders of different pathogenesis, they subdivide this syndrome into four categories: a) neuroacanthocytosis with normal lipoproteins, where our cases would be placed; b) neuroacanthocytosis with hypobetalipoproteinemia; c) neuroacanthocytosis with abetalipoproteinemia, and d) X-linked neuroacanthocytosis, or McLeod's syndrome. These authors also observed that a long follow-up of cases of the first group (neuroacanthocytosis with normal lipoproteins) may disclose a change in the clinical picture, with replacement of the choreic movements by rigidity of limbs, mask face and areflexia. They consider that cases of chorea-acanthocytosis are part of a syndrome that includes familial tic disorder, parkinsonism, motor neuron disease and acanthocytosis. Sakai et al[17] also described one case of a patient with chorea-acanthocytosis that showed a clinical course starting with hyperkinesia, followed by hypokinesia.

Spencer et al[18] reported a variant of the chorea-acanthocyto-

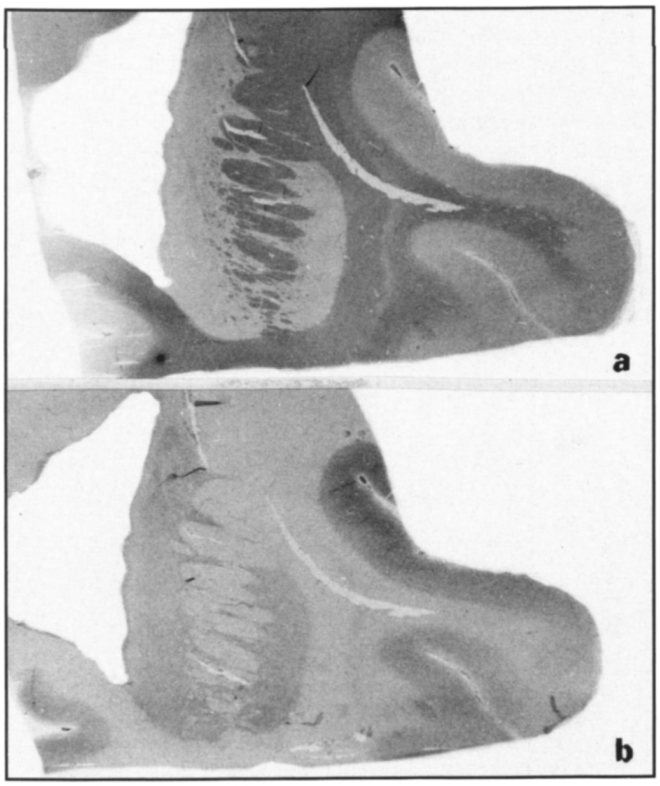

Figure 7A — Atrophy of the head of caudate nuclei (CN) is depicted in this panoramic view of a section at the level of rostral portions of corpus callosum. Klüver Barrera technique × 4. B — Positive staining of caudate and putamen nuclei with Holzer stain for glia.

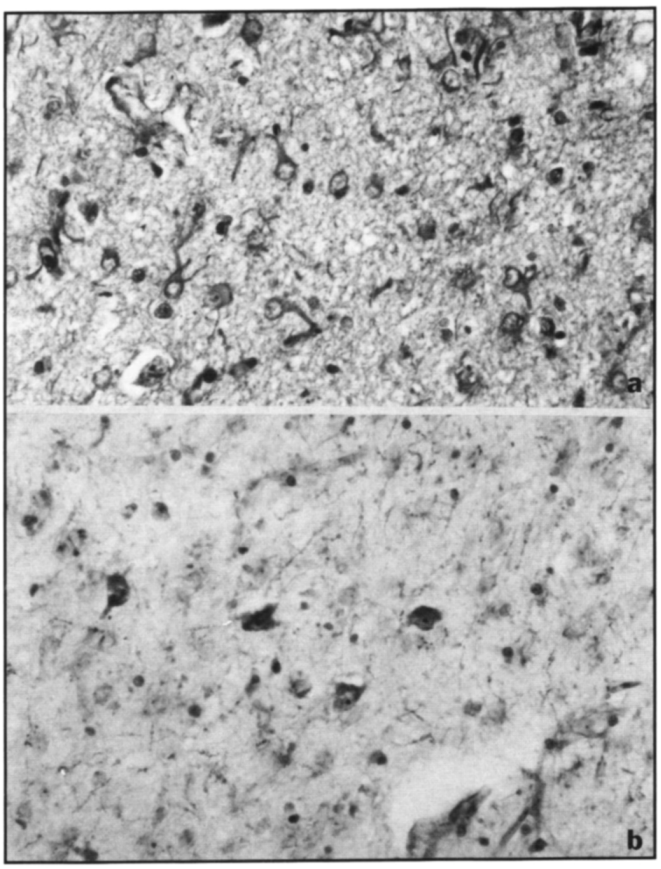

Figure 8A — Astrocytic gliosis in the head of CN. Holzer stain. B — Photomicrographs shows scanty neurons population in the head of the CN. Notice total absence of parvicellular component.

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sis with chronic hemolytic anemia.

Future follow-up of the patients and better knowledge of the neurological alterations associated with acanthocytosis will reveal if they are really different problems, or variants of the same disorder.

References

1. Herbert PN, Assmann G, Gotto AM, Fredrickson DS. Familial lipoprotein deficiency: abetalipoproteinemia, hypobetalipoproteinemia and Tangier disease. *In*: Stanbury JB, Wyngaarden JB, Fredickson DS, Goldstein JL, Brown MS, eds. Metabolic basis of inherited disease. McGraw-Hill Book Company, New York, 1983; 589-621.
2. Estes JE, Morley TJ, Levine IM, Emerson CP. A new hereditary acanthocytosis syndrome. Amer J Med 1967; 42: 868-881.
3. Levine IM, Estes JW, Looney JM. Hereditary neurological disease with acanthocytosis. Arch Neurol 1968; 19: 403-409.
4. Bird TD, Cederbaum S, Valpey RW, Stahl WL. Familial degeneration of the basal ganglia with acanthocytosis: a clinical, neuropathological and neurochemical study. Ann Neurol 1978; 3: 253-258.
5. Dubowitz V, Brooke MH. Muscle biopsy: a modern approach Ch 4 p 100 W.B. Saunders Co Ltd, London 1973.
6. Brooke MH, Engel WK. The histographic analysis of human muscle biopsies with regard to fibre types. Neurology 1969; 19: 378-393.
7. Kito S, Itoga E, Hiroshige Y, Matsumoto N, Muva SA. Pedigree of amyotrophic chorea with acanthocytosis. Arch Neurol 1980; 37: 514-517.
8. Sakai T, Mawatari S, Iwashita H, Goto I, Kuroiwa Y. Chorea-acanthocytosis clues to clinical diagnosis. Arch Neurol 1981; 38: 335-338.
9. Critchley EMR, Clarck DB, Wilker A. Acanthocytosis and neurological disorder without betalipoproteinemia. Arch Neurol 1968; 134-140.
10. Critchley EMR, Nicholson JT, Betts JJ, Weatherall DJ. Acanthocytosis, normolipoproteinemia and multiple tics. Post graduate Med J 1970; 46: 698-701.
11. Amminoff MJ. Acanthocytosis and neurological disease. Brain 1972; 95: 749-760.
12. Ohnishi A, Soto Y, Nagara H, Sakai T, Iwashita H, Kuroiwa Y, Nakamura T, Shida K. Neurogenic muscular atrophy and low density of large myelinated fibres of sural nerve in chorea-acanthocytosis. J Neurol Neurosurg Psychiat 1981; 44: 645-648.
13. Limos LC, Ohnishi A, Sakai T, Fujii N, Goto I, Kuroiwa Y. "Myopathic" changes in chorea acanthocytosis. Neurol Sci 1982; 55: 49-58.
14. Gross KB, Skrivanek JA, Carlson KC, Kaufman DM. Familial amyotrophic chorea with acanthocytosis. Arch Neurol 1985; 42: 753-756.
15. Schwartz SA, Marsh WL, Symmans A, et al. New clinical features of McLeod syndrome. Abstracted Transfusion 1982; 22: 404.
16. Spitz MC, Jankovic J, Killan J. Familial tic disorder, parkinsonism, motor neuron disease and acanthocytosis: a new syndrome. Neurology 1985; 35: 366-370.
17. Sakai T, Iwashita H, Kakugawa M. Neuroacanthocytosis syndrome and choreoacanthocytosis: Levine-Critchley syndrome. Neurology 1985; 35: 1679.
18. Spencer SE, Walker FO, Moore SA. Chorea-amyotrophy with chronic hemolytic anemia: a variant of chorea-amyotrophy with acanthocytosis. Neurology 1987; 37: 645-649.