Available online at www.sciencedirect.com

SCIENCE DIRECT

Surgical Neurology 64 (2005) 542–545

SURGICAL NEUROLOGY

www.surgicalneurology-online.com

Infection

Creutzfeldt-Jakob disease acquired via a dural graft: failure of therapy with quinacrine and chlorpromazine

Juan F. Martínez-Lage, MD[a,*], Alberto Rábano, MD[e], Juan Bermejo, MD[b], Miguel Martínez Pérez, MD[a], M. Carmen Guerrero, MD[e], M. Angeles Contreras, MD[c], Alberto Lunar, MD[d]

Services of [a]*Neurosurgery,* [b]*Pathology,* [c]*Neurology, and* [d]*Clinical Neurophysiology, "Virgen de la Arrixaca" University Hospital, Murcia, Spain*
[e]*Laboratory of Neuropathology, Fundación Hospital Alcorcón, 28922 Alcorcón, Madrid, Spain*

Received 6 December 2004; accepted 21 March 2005

Abstract

Background: Accidental transmission of Creutzfeldt-Jakob disease (CJD) has been reported after neurosurgical interventions, use of intracerebral electrodes, corneal transplants, and after the administration of human-derived hormones. Acquired CJD has also been documented after dural grafting with tissues of human cadaver origin. At present, quinacrine and chlorpromazine are being investigated for the treatment of sporadic CJD, with the hope of offering an effective treatment of an otherwise fatal disease. Our objective was to report a case of iatrogenic CJD occurring 18 years after the implant of a dural graft of human origin and to inform on the results of the treatment with quinacrine and chlorpromazine.

Case Description: In 1984, a 46-year-old woman was given a Lyodura graft for decompression of Chiari I malformation and syringomyelia. The patient was diagnosed with CJD in 2002. In view of the scarce options for treatment of CJD and after reviewing the current literature, the patient was treated with quinacrine and chlorpromazine. She showed no clinical improvement and died 6 months after hospital admission. The iatrogenic origin of the disease in this patient is supported by the clinical features, laboratory data, and findings from the brain necropsy.

Conclusions: Patients who have received a dural graft of cadaveric origin may be at risk for developing CJD after very prolonged incubation periods. Treatment with quinacrine and chlorpromazine for acquired CJD was ineffective in our patient. A clinical trial on the use of antiprion agents is warranted.

Keywords: Chiari I malformation; Creutzfeldt-Jakob disease; Dura mater grafts; Acquired prion diseases; Quinacrine; Chlorpromazine

1. Introduction

Iatrogenic Creutzfeldt-Jakob disease (CJD) because of a corneal transplant from a donor who died of unsuspected CJD was first reported by Duffy et al in 1974 [10]. Bernoulli et al [1] documented 2 cases of CJD acquired through the placement of intracerebral electroencephalograph (EEG) electrodes. In 1985, the first cases of CJD acquired from pituitary hormones of cadaveric origin were reported [15]. After the first description of CJD transmitted via a dural graft of human extraction in 1987, 168 further cases have been reported worldwide (Refs [3-6,8,17,18,22] and P. Brown, personal communication, 2004). The accidental spread of prion diseases prompted the search of preventive measures that, at present, have proven to be effective in halting the spread of the disease [23]. Some treatments for CJD have been essayed with disparate results [7,12-14,16,19,20]. Quinacrine, an antimalarial agent, and chlorpromazine, an antipsychotic drug, have been found to inhibit prion

* Corresponding author. Tel.: +34 968 369489; fax: +34 968 369678.
E-mail address: juanf.martinezlage@cablemurcia.com (J.F. Martínez-Lage).

0090-3019/$ – see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.surneu.2005.03.035

development in experiments and have been used with variable results in a few cases of human prionic diseases, mainly in cases of sporadic CJD [14,16,19]. These 2 drugs have rarely been used in iatrogenic forms of CJD [14].

In this work, we briefly report the clinical findings and the results of treatment with quinacrine and chlorpromazine in a patient with CJD acquired via a dural graft. In view of the scarce reports on these treatments in iatrogenic CJD [14], we think that our report constitutes a valuable addition to the knowledge of the natural history of accidental CJD and to the assessment of currently used treatments for this form of the disease.

2. Case report

A 28-year-old woman was first seen with occipital headaches and weakness in her right hand for the previous 3 years. She had also noted weakness on her left hand and loss of temperature perception in both upper limbs for the preceding year. She recalled having had an occipital head trauma after an episode of syncope that occurred 3 years before. On examination, the patient was conscious and oriented; her fundi were normal and had a mild right ptosis. She had also weakness in both hands, with loss of deep reflexes in her left upper limb. There was sensory loss for temperature and pain in both hands. No abnormalities were seen in the remainder of the woman's physical examination. Neuroimaging studies, which consisted of plain radiographs, computed tomography, and myelography, showed platybasia, descent of the cerebellar tonsils, and widening of the cervical spinal cord. On January 31, 1984, the patient underwent suboccipital craniectomy and laminectomy of C1 to C2. The cerebellar tonsils were descended up to the upper border of C3. Decompression was achieved with a patch of commercially available lyophilized dura mater (Lyodura, Braun Melsungen, Melsungen, Germany). The postoperative period elapsed with a mild meningeal reaction.

The patient was readmitted to the hospital in January 2002, at age 46, complaining of intense dizziness and occasional headaches, together with weakness in all 4 limbs for the previous year. She also described having itching sensations in both hands. She was under treatment of depression. On initial examination, the patient was conscious, had a right Horner sign, and exhibited weakness and hyperreflexia in both legs. The previously described signs of spinal cord involvement in the arms were unchanged. Magnetic resonance imaging demonstrated adequate decompression of the posterior fossa structures, being the cerebellar tonsils in a normal position, and the previously noted cervicothoracic syringomyelia.

After hospital admission, the patient's condition deteriorated; she went into vigil coma and started to show generalized myoclonus. Determination of cerebrospinal fluid protein 14.3.3 was positive. Study of the prion protein (PrP) gene did not show any of the known mutations reported for the genetic forms of CJD. Analysis of codon 129 revealed that the patient was homozygous for methionine/methionine. Serial computed tomography showed a progressive evolution to cerebral atrophy. EEG recording revealed generalized slowing of cerebral activity at the initial stages and periodic activity during the progression of the disease.

Quinacrine at a dose of 300 mg/d was given enterally for 3 weeks. The treatment was complicated by liver dysfunction, yellowish skin, and mucous membrane pigmentation. A further course of chlorpromazine (300 mg/d) was completed. After these treatments, the patient exhibited no clinical improvement. Six months after hospital discharge, the patient died.

Postmortem examination was performed at the Laboratory of Neuropathology of the Fundación Hospital Alcorcón, Madrid (the Spanish national center of reference for the study of prionic diseases [A.R. and M.C.G.]). The brain weighed 1038 g. There was marked cortical atrophy at the cerebral convexities and the cerebellum. Cuts corresponding to several cerebral, cerebellar, and brain stem regions were treated with hematoxylin-eosin, periodic acid–Schiff stain, and Nissl stains and with 3F4 monoclonal acid for the detection of the PrP. In the studied areas, there was vacuolization of the neuropil, astrocytosis, and loss of neurons varying in intensity in the different areas. There were neither neuritic plaques nor Lewy bodies, or other specific features of neurodegenerative diseases. There were deposits of PrP (synaptic pattern) in the neocortex, basal ganglia and cerebellum. No kuru-type plaques were identified in the examined regions. The diagnosis was confirmatory of CJD.

3. Discussion

3.1. Acquired prion diseases

Prion diseases encompass a group of infectious, neurodegenerative, and fatal disorders and include, among others, CJD and kuru in humans, bovine spongiform encephalopathy in cattle, and scrapie in sheep [4,11,21]. The causative agent is an abnormally folded form of the cellular PrP that accumulates in the brain of the affected organisms [21]. Prion diseases in man may develop in 3 ways: (a) sporadic, as happens in CJD, (b) genetic (familial CJD, fatal familial insomnia, and Gerstmann-Sträussler-Scheinker syndrome), and (c) infectious (new variant of CJD and the iatrogenic forms of CJD) [4,6,21]. CJD has been documented after the use of contaminated EEG electrodes and neurosurgical instruments, growth hormone, and gonadotropins of cadaver extraction and after the implant of human-derived dura mater grafts [1-8,10,15,17,18,22]. Hormone-related CJD has been reported in 184 patients who were given growth hormone or gonadotropins, chiefly in France, United Kingdom, United States, and Australia [2,6,16]. This mechanism of prion transmission has been termed as "peripheral" route. In cases of CJD related to contaminated