Differential diagnosis of prion diseases in the vast chapter of degenerative encephalopathies, a challenge for the internist: two case reports compared

Filomena Pietrantonio,[1,2] Angela Ciamei,[1] Gabriele Angelo Vassallo,[3] Luca Moriconi,[4] Margherita Lordi[5]

[1]Internal Medicine Unit, Medical Area Department, Ospedale dei Castelli, Local Health Authority Roma 6, Rome; [2]St. Camillus University of Health Sciences, Rome; [3]Barone Lombardo Hospital, Canicattì; [4]Internal Medicine Unit, Local Health Authority Rieti Medical Department, S. Camillo De Lellis Hospital, Rieti; [5]Geriatric Intensive Care Unit, AOU Careggi di Firenze, Florence, Italy

ABSTRACT

Prion diseases, or transmissible spongiform encephalopathies, fall under the big chapter of differential diagnosis of degenerative diseases of the central nervous system. The cause is prions, which are altered forms of the prion protein (PrP). In pathology, PrP changes its form, becoming a prion, *i.e.*, an infectious protein capable of inducing normal PrP to assume the pathological form. The accumulation of PrP in brain cells creates very small bubbles (vacuoles) that lead to the formation of microscopic holes that make the brain tissue resemble a sponge (hence the term spongiform encephalopathies). These are very rare diseases with a very long latency. After the first symptoms appear, the disease evolves rapidly. There is no treatment, and the outcome is often inauspicious. Two clinical cases of prion disease occasionally found in patients admitted from emergency rooms to the Department of Internal Medicine are described.

Correspondence: Filomena Pietrantonio, Internal Medicine Unit, Medical Area Department, Ospedale dei Castelli, Local Health Authority Roma 6, Rome, Italy.
E-mail: filomena.pietrantonio@gmail.com

Key words: prion diseases, degenerative encephalopathies, differential diagnosis, internal medicine role, research model.

Contributions: FP, ML, conceptualization, methodology, writing – original draft, writing – review and editing; ML, AC, data curation, investigation; FP, LM, formal analysis; FP, resources, supervision; FP, GAV, validation; LM, visualization. All authors have read and agreed to the published version of the manuscript.

Conflict of interest: the authors declare that they have no competing interests.

Ethics approval and consent to participate: not applicable.

Patient consent for publication: informed consent was signed by the patients.

Availability of data and materials: the datasets used and/or analyzed during the current study are available upon reasonable request from the corresponding author.

Funding: none.

Acknowledgments: the authors acknowledge Ann Elizabeth Tilley for her valuable contribution to the English revision.

Received: 7 June 2025.
Accepted: 17 June 2025.
Early view: 23 June 2025.

Publisher's note: all claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher.

Licensee PAGEPress, Italy
Italian Journal of Medicine 2025; 19:2075
doi:10.4081/itjm.2025.2075

Introduction

Prion diseases or transmissible spongiform encephalopathies are a group of slowly progressive and consistently fatal neurodegenerative diseases described in both animals and humans.[1,2] Prion disease results from the misfolding of a normal cell surface protein called cellular prion protein (PrP). Misfolded PrPs are called prions or scrapie PrP (PrP, after the prototypical sheep prion). PrP is pathogenic and transmissible. Normal PrP is water-soluble and sensitive to protease, but a large percentage of PrP is water-insoluble and remarkably resistant to protease degradation [as is the case with β-amyloid plaques in Alzheimer's disease (AD), which PrP resembles]; there will be a slow but relentless cellular accumulation of PrP, resulting in the induction of cell death. This is accompanied by gliosis and the formation of characteristic vacuoles (spongiform tissue), resulting in dementia and other neurological deficits. Prion diseases are classified as sporadic, familial, and infectious.[3] Two clinical cases of prion disease found occasionally in patients admitted from the Emergency Department (ED) to the Department of Internal Medicine are described.

Case Report 1

A 55-year-old male was admitted to the ED for psychomotor agitation and paranoid ideation. In the anamnesis: history of known psychiatric pathology under treatment with psy-

chotropic drugs. Blood tests, an electrocardiogram, and a chest X-ray were performed within limits. The brain computerized axial tomography (CT scan) showed lacunar ischemic sequelae and cortico-subcortical atrophy phenomena. A psychiatric consultation was performed. During the interview with the psychiatrist, the patient appeared well-groomed in appearance, sufficiently accessible, and collaborative. Dysphoric mood, fluid speech, and mobile facial expressions and gestures were observed. The thought presented a loosening of associative links, up to frank ideic dissociation. Difficulty in adequately answering questions was evident, showing derailment of thought and logical leaps. Poor awareness of state was observed, as well as a moderate amount of anxiety. The patient presented with intact sensorium and denied anti-conservative and hetero-aggressive ideas and/or intentions. The reported psychiatric history was mute up to 2 years prior, a period in which the current psychiatric symptoms appeared when, 2 months prior, he turned to a private psychiatrist who prescribed valproate, pregabalin, and quetiapine, therapy still in progress. No indication for hospitalization in a psychiatric specialist environment was given. The following indications were given: promazine intramuscular in case of psychomotor agitation, blood valproate dosage (which was at the upper limits), ammonium (which was in range), and a request for neurological evaluation. At the neurological visit, no pyramidal or extrapyramidal signs, and no focal deficit were observed. During hospitalization in an internal medicine setting, the following tests were executed: supra-aortic trunk ecodoppler (TSA), echocardiogram (EcoTT), electroencephalogram (EEG), lipid profile, vitamin profile, thyroid profile, glycated hemoglobin, and magnetic resonance imaging (MRI) of the brain and brainstem with and without contrast medium (Figure 1). The patient was transferred to Internal Medicine. The anamnestic collection was completed with the patient's wife, who reported the onset of symptoms starting from 2 years before. The patient complained of deficits in recent memory that progressively worsened. These had been associated with mood disorders and behavioral changes with ideas of reference, delusional ideas, and obsessive behaviors. The patient always presented full awareness of the difficulties, tracing his symptoms back to those of his father, who suffered from bipolar disorder. Fearing that he too was affected by this pathology, he underwent a psychiatric evaluation 2 months before, starting therapy with little benefit. During hospitalization, the patient presented concentration and attention deficits, very poor speech, which on some occasions became incomprehensible, with anomies and paraphasia (mainly phonetic).The month before, the patient reported having heard voices that ordered him to turn while he was driving, responsible for an accident (no head trauma or loss of consciousness reported). In these months, the patient has always maintained adequate attention to personal hygiene and personal care with substantial maintenance of levels of autonomy. The reason that pushed the patient's wife to go to the emergency room (ER) was a worsening behavior with hetero-directed physical aggression. A few days before accessing the ER, a brain MRI without contrast medium was performed, with the identification of hyperintense areas in the bifrontal area and bilateral areas of a nonspecific/vascular nature. In the department, the tests requested by the neurologist were carried out and all were within normal limits except for the MRI with and without contrast medium which shows findings that suggest the diagnostic hypothesis of an initial neurodegenerative form such as AD or corticobasal degeneration "... substantially symmetrical enlargement of the Sylvian fissures with increased representation of the cortical sulci, more evident in the fronto-temporo-parietal area on both sides, in relation to reduced tissue tropism... enlargement of the temporal horn, in relation to reduced tropism of the hippocampus of both cerebral hemispheres, with a slightly more evident finding on the right... alteration of the signal, hyperintense in the T2-weighted sequences involving both hippocampi, in particular the body-tail on the right... Slight reduction of the tropism of the head of both caudate nuclei, with a slightly hyperintense signal... right. The corpus callosum is thinned in its entirety. The mesencephalon is slightly thinned. Some sporadic and millimetric areas of T2-T2 FLAIR signal hyperintensity are documented in the periventricular, juxta, and subcortical fronto-parieto-insular white matter of both cerebral hemispheres, of nonspecific gliotic significance. Non-pathological restrictions of diffusivity in the brain tissues. In the right external capsule, two punctate drops in signal are evident in the magnetic susceptibility sequences, in relation to hemosiderin deposits... Non-pathological enhancement in the endocranial area...". A neurological reassessment was performed, which indicated a diagnostic spinal tap (film array, metaphysical, cytochemical, and all screening for any paraneoplastic, immune-mediated, and prion pathologies on the cerebrospinal fluid: prot 14-3-3 research; prot real-time-quaking-induced conversion (RT-QuIC) research; codon 129 polymorphism of *PRNP* gene and mutation screening, sample sent to the *Istituto Superiore di Sanità* (ISS). All tests were negative except for the positivity of the RT-QuiC, which supports the clinical suspicion of Creutzfeldt-Jakob disease.

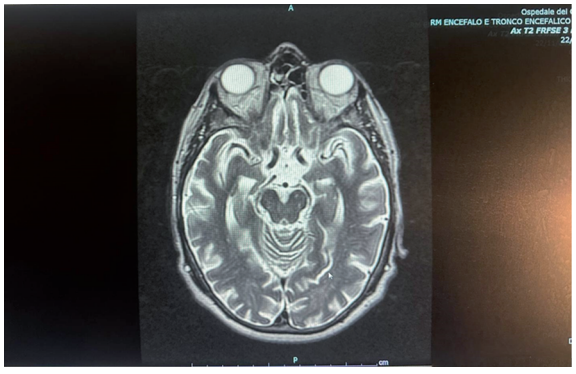

Figure 1. Magnetic resonance imaging of the brain of patient 1.

Case Report 2

A 56-year-old female was admitted to the ER for a fall to the ground with full consciousness; the patient reported disturbance of balance for about 3 months and dysarthria for 3 weeks. In anamnesis: previous left cerebral venous thrombosis and right cerebral ischemia, secondary epilepsy, favism, removal of reported benign ovarian cysts, and previous right lower limb ulcer. The patient was on home pharmacological therapy with Coumadin, according to the international normalized ratio, and levetiracetam. Upon admission to the ER, the patient appeared alert, poorly oriented in space and time, mild nystagmus (NY). Blood tests, chest X-ray, ECG, and skull-brain CT without contrast medium were performed (the

patient refused the contrast medium); the tests performed were all within normal limits. A neurological consultation was performed that recommended performing a brain MRI with intracranial arterial and venous angio MRI in an internal medicine hospital setting, with subsequent neurological reassessment. The patient was therefore transferred to Internal Medicine. Upon admission, vital parameters were detected within limits. The patient appeared in mediocre general conditions, ataxic, dysarthric, with mild convergent strabismus, with NY in the lateral gaze to the left but without oculomotor deficit or diplopia. She maintained the Mingazzini with a single lower limb without gross deficits in strength; she maintained an antigravity position with the upper limbs without deficits in strength and dysmetria on the index-nose tests bilaterally, more on the right. The patient presented the following physical examination: tongue in axis; cardiac activity rhythmic and with normal frequency, distant tones. On chest auscultation, a vesicular murmur was present, with fine crepitations. The abdomen was globose, not painful, with valid peristalsis. Neurological objectivity appeared normal without a deficit of the cranial nerves. Tendon reflexes were bilaterally symmetrical on the four limbs. Plantar reflex in bilateral flexion. The following tests were requested: blood tests, brain MRI with contrast medium and cervical spinal cord with intracranial venous and arterial MRI, EcoTT, standard EEG, TSA ecodoppler, coagulation factors, homocysteinemia, and speech therapy video. The following tests were all within limits except for the EcoTT (which showed an interatrial septum flagging but apparently without shunt) and the brain MRI with angio-MR: "…focal signal alteration, hyperintense in T2 and FLAIR sequences and characterized by marked restriction of diffusivity, involving the putamen and the caudate nucleus in a bilateral and symmetric manner; concomitant analogous signal alteration in the bilateral fronto-parietal para-focal cortical area, more evident on the right and at the level of the temporo-occipital gyrus and right parahippocampal. Millimetric hyperintense focus in T2 and FLAIR of nonspecific gliotic significance is appreciable in the right peritrigonal white matter. Concomitant faded signal alteration, hyperintense in T2-FLAIR of the periaqueductal grey matter (Figure 2). The angio-MR study does not show significant visualization defects involving the main vessels …". A neurological reassessment was therefore performed: "the findings described in the supratentorial encephalic area do not appear to have a univocal interpretation, as it is not possible to exclude an alteration of inflammatory-infectious significance (prion disease?), less likely an alteration of toxic-metabolic significance (negative tests); a liquor examination is essential". The patient was therefore subjected to a spinal tap, and the liquor tests sent to the ISS showed a positive search for the PrP, confirming the clinical suspicion of Creutzfeldt-Jakob prion disease.

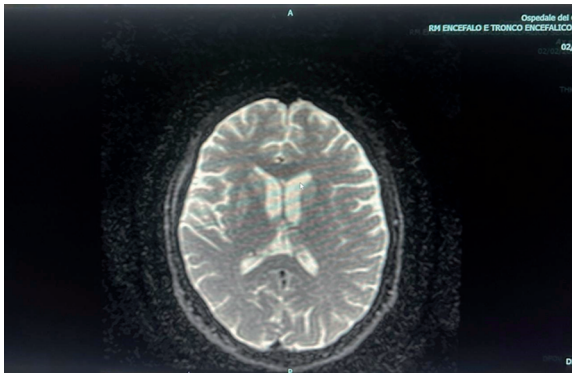

Figure 2. Magnetic resonance imaging of the brain of patient 2.

Discussion

Prion diseases are included in the differential diagnosis of degenerative encephalopathies of the central nervous system. They are rare diseases; however, they should not be forgotten when approaching a patient who presents neurological and behavioral disorders that do not respond to therapy with psychotropic drugs, do not have an identifiable metabolic cause, and do not reflect the diagnostic criteria of the main degenerative encephalopathies, such as AD. The internist often, especially in small to medium hospitals, has the arduous task of acting as an orchestra conductor in organizing the series of tests necessary for the differential diagnosis of these diseases, as the two clinical cases described demonstrate.

Conclusions

Prion diseases should be considered in the differential diagnosis of any adult patient with dementia, atypical movements, or psychiatric manifestations, especially if the progression of symptoms appears rapid.[1,2] These are very rare diseases (incidence is 1-2 cases per million/year), difficult to diagnose differentially, with a very long latency. After the appearance of the first symptoms, the disease evolves rapidly. Treatment is supportive. There is no treatment, and the outcome is often fatal.[4] However, they remain an exciting research model because they belong at the same time to the group of neurodegenerative diseases due to protein storage, to the group of transmissible diseases, but also to the group of genetic diseases, since some of them are Mendelian dominant in transmission.[5,6]

References

1. Doria R, Menichetti F. Prion diseases. Infez Med 2001;9:72-81. [Article in Italian].
2. Ladogana A, Puopolo M, Croes EA, et al. Mortality from Creutzfeldt-Jakob disease and related disorders in Europe, Australia, and Canada. Neurology 2005;64: 1586-91.
3. Appleby B. Panoramica sulle malattie prioniche (Encefalopatie spongiformi trasmissibili). 2024. Available from: https://www.msdmanuals.com/it/professionale /malattie-neurologiche/malattie-prioniche/panoramica-sulle-malattie-prioniche.
4. Istituto di Ricerche farmacologiche Mario Negri. Malattie da prioni: cause, diagnosi e potenziali terapie. Available from: https://www.marionegri.it/magazine/ malattie-da-prioni.
5. Brandel JP, Haïk S. Malattie da prioni o encefalopatie spongiformi trasmissibili. EMC - Neurologia 2016;16: 1-21.
6. Will RG, Ironside JW, Zeidler M, et al. A new variant of Creutzfeldt-Jakob disease in the UK. Lancet 1996;347: 921-5.