# Human prion disease in Piemonte and Valle d’Aosta, Italy: the experience of the reference center for human prion disease and a case description.

European Society of Pathology

# 30th European Congress of Pathology

*Pathology: Path to Precision medicine*

**8 – 12 September 2018,** Euskalduna Conference Centre, Bilbao, Spain

## Disclosure Information

I hereby declare that I have had business or personal interests in the following industrial enterprises since 1 September 2017:

**Name of the enterprise / Nature of the interest**

| Enterprise \| Interest |
| --- |
| None |

# Introduction

- The “Centro regionale Diagnosi Osservazione Malattie Prioniche (DOMP)” is the reference center for the diagnosis and the surveillance of human prion diseases in Piemonte district, North West Italy. The DOMP center is active since 2002 and is organized in a multidisciplinary framework in which clinico-pathological expertise and laboratory tests to get *in vitam* and *post-mortem* diagnosis of Creutzfeldt-Jakob disease (CJD) and related syndromes are available. In particular, the DOMP center offer cerebrospinal fluid (CSF), biochemical, neuropathological and genetic investigations necessary to neurologic units of Piemonte hospitals.
- Hereby, we describe a very rare case of genetic CJD due to the E196K mutation of the prion protein (PRNP) gene in which the comprehensive approach of DOMP center succeed in the right classification.

# Clinico-pathological description

- A 85-year-old man with a 2-month history of short-term memory deficits and fluctuating confusion came to our observation in 2015. Neurologic examination at admission disclosed only a mild temporal disorientation with bilateral cerebellar dysmetria with dysdiadochokinesia and gait unbalance. Moreover, rare myoclonic jerks were evident. The brain MRI only highlighted mild cortical atrophy with evidence of diffuse vascular damage whereas the EEG pattern was possibly suggestive of a prion disease since the inconstant occurrence of bilateral periodic sharp wave complexes.
- CSF analysis showed the presence of 14.3.3 protein. Total tau, phosphorylated tau and ABeta-42 levels in CSF were 994 pg/ml (n.v. <500 pg/ml), 49 pg/ml (n.v. <61 pg/ml) and 260 pg/ml (n.v. <500 pg/ml), respectively. The PRNP codon 129 genotyping disclosed a Methionine/Methionine homozygosity.
- A diagnosis of probable Creutzfeldt-Jakob disease was made.
- The clinical picture rapidly deteriorated and the patient became tetraparetic, mutacic and unable of swallowing in a week. He died from a multi-organ failure after 2 weeks from the first hospital admission.
- A brain-limited autopsy was performed to confirm CJD diagnosis.
- Western blot analysis on frozen brain tissue confirmed the diagnosis of CJD since the presence of type 1 PrPres according to Parchi and Gambetti classification. Regarding neuropathologic investigations, on macroscopic examination only a mild diffuse cortical atrophy was evident. Microscopic examination disclosed relevant spongiform changes involving all cortical layers with concomitant gliosis and neuronal loss. Gliosis was also evident in basal ganglia whereas cerebellum and brainstem were less affected. Immunohistochemistry for protease resistant prion protein (PrPres) was highly positive showing a typical synaptic pattern.
- The disclosure of the definite diagnosis of CJD in the present case led the patient's familiars to ask for ruling out the presence of PRNP gene pathogenic mutations. Therefore, after genetic counselling, ORF gene sequencing was performed on the DNA extracted from frozen brain tissue and, surprisingly, the very uncommon E196K mutation was detected. A final diagnosis of genetic CJD due to E196K was formulated.

# Conclusions

- The described CJD patient represents a very rare genetic case of CJD.
- To the best of our knowledge, less than 20 CJD patients harboring the same mutation are reported in literature. In our opinion there are two peculiar aspects in our patient, at least: first, the very late age of onset and, second, the clinic-pathological phenotype perfectly mimicking a “classical” sporadic case.
- The comprehensive approach of DOMP center, that put together clinical expertise and biochemical neuropathological and genetic investigations, is certainly winning in diagnosis and surveillance of human prion diseases.

# Human Prion Disease Center – Torino
# Casistic (january 2002 – september 2018)

- Overall TSE: 174 patients (80 M)
  - Median age (IQR): 68 (61-73) years

- Sporadic CJD: 120 patients (48 M)
  - Median age (IQR): 70 (65-76) years

- Sporadic Fatal Insomnia (sFI): 2 patients (0 M)

- Overall genetic TSE: 52 patients (28 M)

  [gCJD=46; GSS=5; FFI=1]
  - Median age (IQR): 62 (53-68.25) years

# Human Prion Disease Center – Torino
# Genetic TSE (january 2002 – september 2018)

- fCJD E200K: 25 patients
- fCJD V210I: 13 patients
- fCJD V189I(*): 2 patients
- fCJD D178N: 1 patient
- fCJD E196K: 4 patients
- fCJD V203I: 1 patient
- FFI (D178N): 1 patient
- GSS (P102L): 5 patients

(*) new mutation (manuscript in preparation)