A Case of Subacute Progressive Mutism Syndrome

Presented by Dr Nahid Shamandi

Research for Clinicians Day – November 4th 2021

INTRODUCTION

A 62-year old man with no Significant medical background presented to his GP with 1 month history of worsening speech and language problems who advised he attend the Emergency Department.

On arrival to hospital, he was disoriented to time and place. His initial language problems were difficulties in completing sentences which later progressed to a state of being almost non-verbal.

There was no history of neuro- or ophthalmic surgery, transfusion or transplantation. Past medical history includes hypertension and osteoarthritis.

Family history included one maternal uncle with dementia,, diagnosed in his 60s. His mother died at 66 from metastatic cancer of unknown primary source and his father was alive into old age. All of his six siblings were alive and there was no known family history of neurodegenerative disease.

On examination, there was no obvious facial weakness, visual fields testing to menace had a normal response in all directions. Tone normal in upper limbs. Deep tendon reflexes were present and symmetrically equal. Planters were flexor bilaterally. He was independently mobile with a normal gait. There was no overt myoclonus nor startle response.

01 Investigations

Bloods – unremarkable

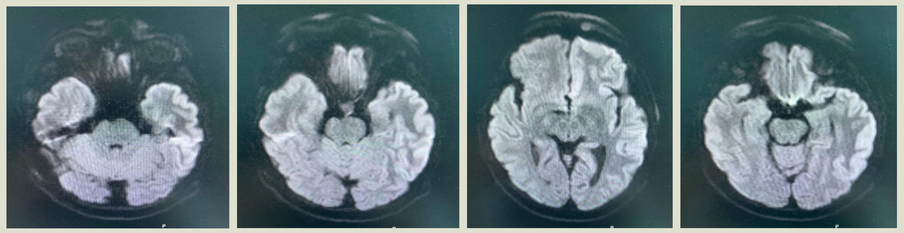
CSF – WCC0, Protein 0.23 g/l.

EEG – Some sharp and 'quasi-periodic' changes have been reported, which were non-specific.

CT brain - No acute intracranial or skull base abnormality.

CT CAP – No definite primary malignancy or metastatic disease identified.

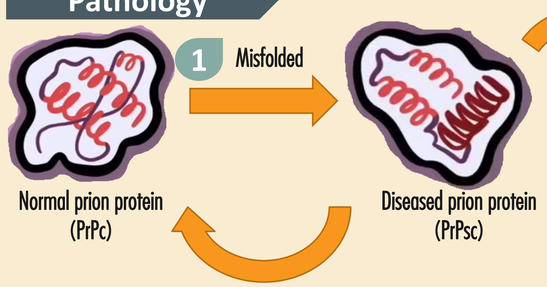
MRI head – Extensive cortical ribboning throughout the left hemisphere, affecting left insular and interhemispheric regions, left frontal, parietal and occipital lobes. A small area of cortical high signal is seen in the right parietal lobe.

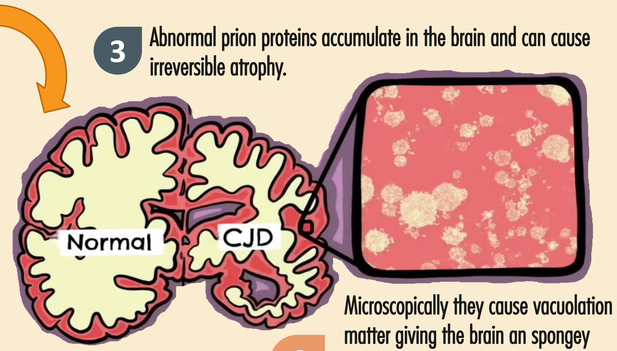


02 Creutzfeldt-Jakob Disease

- Creutzfeldt-Jakob Disease (CJD) is a group of disorders caused by build-up of misfolded prion proteins in the brain.
- Normal prion proteins are a part of nervous system participating in several biological processes including neuronal homeostasis, cell signalling, cell adhesion and protection against stress.

Pathology





Classification

1.Sporadic CJD
- Most common type.
- Most likely cause by a normal brain protein misfolds to create a prion.

2.Variant
- Most likely caused by consuming meat from a cow that had bovine spongiform encephalopathy (mad cow disease).

3. Familial
- A very rare genetic form where one of the prion protein genes carries a mutation that causes prion to form during adulthood.

4. Iatrogenic
- Infection is accidently spread from someone with CJD through medical and surgical treatment (ex. Organ transplant or blood transfusion)

Types of CJD

Presentation

- The presentations of CJD is variable but symptoms are often rapidly progressive.
- 1/3 experience fatigue, sleep disturbance and reduced appetite.
- 1/3 have neurological changes including memory loss, behavioural changes and confusion.
- 1/3 show focal neurological signs such as cerebellar ataxia, aphasia, visual disturbance and motor weakness.

Diagnoses

- It is important to rule out infections and toxicities.
- Definitive diagnosis for CJD is with brain biopsy (post-mortem).
- The second generation of rea-time quaking-induced conversion (RT-QuIC) using CSF is now widely used for the diagnosis of CJD.

03 Treatment & Prognosis

Despite numerous studies, testing the effects of steroids, antiviral agents and antibiotics on prions , so far no treatment has been found to cure or even delay CJD.

Current treatments for CJD is aimed at alleviating symptoms and making the patient as comfortable as possible.

Subject of this study was discharge from hospital with Levetiracetam, Midazolam, Glycopyronium Morphine Sulphate and Cyclizine. Furthermore, he was referred to the community palliative team for follow up and comfort care.

CJD is a very rapid progressive and fatal disease, with a median of survival of 4-6 months and 95% patients succumbing to illness within a year. Our Patient passed away 2 month after being discharged from the hospital. By the end, he was completely non verbal and had progressive weakness in his right side causing inability to mobilise independently.

Empirical treatment :
- IV Methylprednisolone
- Levetiracetam
- Human immunoglobulin (IVIG)

Differential Diagnosis :
- Encephalitis (viral vs bacterial)
- Post seizure related signal changes
- Prion disease

Final diagnoses:
CSF 14-3-3, S100b and RT-QuIC results were consistent with prion disease and hence, patient was diagnosed with sporadic Creutzfeldt-Jakob Disease (CJD) .

04 CONCLUSION

CJD disease was first described by German neurologists, Hans Gerhard Creutzfeldt in 1920 and shortly afterward by Alfons Maria Jakob, giving it the name Creutzfeldt–Jakob. However, it was Stanley Prusiner, an American neurologist, who delved into the riddle of its aetiology and discovered that infectivity was based on a protein present in an abnormal form, capable of forming amyloid structures. In 1982, he proposed a model based on an infectious protein and suggested the name "prion", an acronym derived from "proteinaceous infectious particle" which won him a Nobel Prize in medicine in 1997.

Since then, hundreds of researchers and physicians have continued to shed light on the origin, behaviour and impact of prions responsible for CJD. However, there are still significant gaps in our knowledge, mainly due to difficulties facing such studies. For example, number of cellular models available for studying human prions remains limited and propagating prions in cultured cells have proven to be particularly challenging. This has negatively impacted the discovery of drugs for CJD.

Clinically, CJD is both rare and phenotypically diverse which makes the process of diagnosis difficult and often based on elimination process.

Overall, a long way remain to fully understand and successfully treat CJD. Meanwhile, patients and families affected by this disease should be supported both medically and psychologically.

Resources
1. Baldwin KJ, Correll CM. ***Prion Disease***. Semin Neurol. 2019 Aug;39(4):428-439. doi: 10.1055/s-0039 1687841. Epub 2019 Sep 18. PMID: 31533183.
2. Knight R. ***Clinical diagnosis of human prion disease***. Prog Mol Biol Transl Sci. 2020;175:1-18. doi: 10.1016/bs.pmbts.2020.07.006. Epub 2020 Aug 24. PMID: 32958229.
3. Ma J, Wang F. ***Prion disease and the 'protein-only hypothesis***'. Essays Biochem. 2014;56:181-91. doi: 10.1042/bse0560181. PMID: 25131595; PMCID: PMC6760854.
4. Sigurdson CJ, Bartz JC, Glatzel M. ***Cellular and Molecular Mechanisms of Prion Disease***. Annu Rev Pathol. 2019 Jan 24;14:497-516. doi: 10.1146/annurev-pathmechdis-012418-013109. Epub 2018 Oct 24. PMID: 30355150.

Acknowledgment

I would like to sincerely thank our patient's family who generously allowed me to share his journey.