Rapidly Progressive Dementia

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- Male 60 years old.
- DM 5 years ago.
- At Jan 010 amnesia for names and recent events, progressive in last three months.
- Neurological exam.: NAD but low MMSE.
- Prescription of aspirin and donepezil.
- Two months later still memory deteriorated.
Five gram MP followed by oral tapering for two weeks plus oral zovirax for 4 weeks.
Evaluation 1.5 ms later showed more mental deterioration with impaired daily life activities but no neurological deficits.

WHAT TO DO? and WHAT TO SAY?
We are in front of RPD
Memantin was added to ttt.

Lab. For RPD:
- ESR: 22 mm/hr and normal immunology profile.
- Normal tumor markers.
- Normal Thyroid functions.
- Normal CT chest and abdomen.
- CSF, normal cells, normal protein.
- Negative PCR for CMV and HSV.
Seven settings of PE.

One month later (sept. 010) the patient showed stepwise worsening.

Marked mental deterioration and become sleepy and cannot walk.

On exam.: right side weakness.
The biopsy showed evidence of glioblastoma multiformis.

Gliomatosis cerebri or multicentric glioma.
Rapidly Progressive Dementia:

- No standard definition of RPD.
- Dementia with accelerated rate of decline, that progress from first symptom to dementia in less than one year.
- Vast majority of publications are case reports.
- Variable prognosis depending on the underlying cause.

(Geschwind et al 2008)

Untreatable causes:
- Creutzfeldt-Jakob disease, and other prion diseases.
- Degenerative conditions (AD, mixed, LBD, FTD, PSP, CBGD)

Treatable causes:
- Immunological (LE, HT, vasculitis etc)
- Malignant (tumor, paraneoplastic)
- Endocrinal (hypothyriodism, HT)
- Toxic and metabolic: alcohol, methymalonic acidemia, organ failure.
- Infections (HIV, fungal)

UCSF cohort 2008
Creutzfeldt-Jakob disease:

- Incidence, 1–2/ million/year. (Miller 2009)
- sCJD (85%):
  - Age: 50-70.
  - Survival is 5 months. (Geschwind et al 2008).
- vCJD (1%):
  - Age of 29 years.
  - Presents with a psychiatric prodrome.
  - Lasting > 6 months. (Zeidler 2000).
- Familial CJD (15%):
  - AD affect PRNP in chromosome 20.
  (Geschwind 2007)

Diagnostic Criteria for Probable CJD:

- Rapidly progressive dementia
- At least 2 out of 4 clinical features:
  (i) Myoclonus
  (ii) Visual or cerebellar signs
  (iii) Pyramidal/extrapyramidal signs
  (iv) Akinetic mutism
- A positive result on at least one of:
  (i) Typical EEG (periodic sharp wave complexes) during an illness of any duration
  (ii) Positive 14-3-3 CSF assay in patients with disease duration of less than 2 years
  (iii) MRI high signal abnormalities in caudate nucleus and/or putamen on DWI or FLAIR.
Brain MRI in CJD:

- Sensitive (92%) and specific (94%) diagnostic tool for CJD. (Shiga et al. 2004)
- Typically: FLAIR and DWI hyperintensities involving Caudate and putamen and may cortical (alone in 25%).
- Corresponding ADC hypointensity is further supportive of sCJD.
- vCJD is characterized by the “pulvinar sign” hyperintensities affecting the pulvinar nucleus on T2 and FLAIR. (Zeidler et al. 2000)
● **CSF profile in CJD:**
  - Mildly elevated protein.
  - Normal glucose.
  - No leucocytosis.
  - 14-3-3 protein (50%), OCBs, tau, and NSE

● **EEG changes:**
  - Focal or diffuse slowing in early stages.
  - Characteristic 1–2 Hz periodic sharp waves be present in later stages.
  - Sensitivity 55% and specificity 80%.

(Geschwind 2008)
- Female 23 years.
- Started in Apr. 010, with abnormal behavioral changes with some delusions.
- Psychiatric ttt for three months.
- Progressed with disequilibrium, myoclonus, and difficult concentration.
- Ex.: pyramidal, and cerebellar extrapyramidal signs.
• Serum copper, ceruloplasmin and 24 hours urine copper was normal.
• Serum Lactate and pyruvate was normal.
• EEG showed mild diffuse slow background, no periodic pattern.
• CSF exam. Is normal but no protein14,3,3.
• So diagnosed as propable vCJD.
• Deteriorated to bed ridden with bed sores and died 14 ms after her first symptom.

Neurodegenerative disease:
• The second common cause (17- 35% ) of RPD.
• CBD, FTD-MND and DLB may present with an accelerated time course, with behavioral and psychiatric symptoms as well as with myoclonus and extrapyramidal findings.
• More susceptible to metabolic and infectious disturbances causing rapid deterioration.

(Geschwind etal 2007)
**Diagnosis:**

- By exclusion and requires comprehensive serum and CSF analyses and neuroimaging.

- Atrophy patterns on MRI can distinguish various causes of dementia.

(Seeley et al 2009)
Autoimmune limbic encephalitis:

- An autoimmune disease of the brain associated with antineuronal antibodies that cause limbic encephalopathy.
- Paraneoplastic: antibodies react against proteins expressed by the tumor. Precede the neoplasm in 70% of cases.
- Non-paraneoplastic.

(McKeon et al 2007)

- Present with subacute short-term memory loss.
- Other cognitive and behavioral symptoms such as executive dysfunction, personality changes, panic attacks, delusions, seizures and hallucinations have been described.

(Vincent et al 2004)
• **Evaluation:**
  - Detection of underlying tumor.
  - Detection of antibodies, anti-Hu, CV2, Ma2, NMDA, AMPA and VGKC.
  - Exclude other infective LE as HS, &HIV by CSF examination and PCR.
  - MRI brain: T2w hyperinensities in medial temporal lobe.
The treatment:

- Focus on addressing the underlying tumor.
- Treatment for VGKC-LE without an underlying tumor involves plasma exchange and/or IVIG followed by oral corticosteroids. (Graus, et al 2007)

Hashimoto’s Encephalopathy (HE):

- Sub-acute autoimmune condition present as a dementia, tremor, myoclonus, visual hallucinations, ataxia, headache, psychosis, and sleep disturbance. (Chong, et al 2003)

Diagnosis:

- Elevated anti-TPO and anti-TG.
- Increased CSF protein (78%).
- EEG may shows diffuse slowing, or periodic triphasic or sharp wave.
MRI show generalized atrophy, PVWM changes, and diffuse increased T2 signal within subcortical and cortical regions.

- Responds to treatment with corticosteroids, plasmapheresis or immunosuppressive therapy.

- Male 33 years.
- No past medical problem.
- At Sep. 011 gradual progressive recent amnesia.
- At Jan. 012 did MRI brain.
- Treated with ginko biloba & memantin
- Still memory deteriorated and associated with some behavioral changes as micturation at the street,
- Consulted many doctors with psychiatric hospital admission.
- Diagnosed as psychotics with rehabilitations program and antipsychotic.
- Still mental function worsening with pit slow in motion.
- Ex.: ataxia, apraxia, aphasia and mild bilateral pyramidal signs.
- Repeat MRI brain and EEG at Jul 012.
**OPINION:**
- The collective data mentioned in view of the patient's age and clinical data are pointing out to sequelae of Creutzfeldt-Jakob disease, which is often caused by prion, which is a proteinaceous infectious particle devoid of DNA and RNA.
- For further correlation and follow up as appropriate.

**V.B.**
- The lack of presence of basal ganglia abnormality does not exclude this diagnosis.

**IMPRESSION:**
- The brain perfusion SPECT study is non-conclusive, although the perfusion pattern is finely non uniform, yet no definite sizeable gross defect seen. MRI assessment is recommended.
- CT and MRI chest and abdomen were normal.

**IMPRESSION:**
- Rectal mural thickening as described likely neoplastic for lower endoscopy.
- Right gluteus maximum lesion likely metastatic.

- Rectal endoscopy is normal.

- Normal Thyroid functions.
- Normal ESR.
- Negative tumor markers.
- Normal full immunological screen.
- Virology: positive CMV and HSV IgG antibodies.
- Negative PCR for HSV and CMV.
- CSF: normal cells, protein IgG index and negative OCBs.
- Dignosed as probable vCJD.
- Worsened, with severe dementia, no speech, ataxia, mixed pyramidal and extrapyramidal more in right side. Incontinence, severe dysphagia.
- Generalized infrequent tonic fits.
- Bid ridden for three months and died at Aug. 013.

**Management of RPD patients:**
- **History** Onset, duration, associated features, comorbid conditions; exposures, medication, systemic disease; travel history, or blood products.

- Collateral history from close relatives; hallucinations, psychosis; fluctuating presentation; family history; headache; weight loss; skin rashes etc.

- Collateral history from other sources; previous hospital admissions, other physicians, workplace; other relatives.
**Examination:**
- Signs of systemic disease;
- Fundus examination;
- Neurological examination for focal signs; rigidity, motor disorders, cerebellar signs, myoclonus.

**Full neuropsychological testing.**

**Lab.:**
- **Chemistry panel:** CBC, RFTs, LFTs Ca, sugar, electrolytes, urine analysis.
- **Reversible dementia panel:** TSH, vit.B12, homocysteine, and methylmalonic acid.
- HIV, VDRL, tumor markers and drug level.
- **Immunology:** Anti-TG, anti-TPO, P-ANCA, C-ANCA; ESR, ANA, CRP.
- **Paraneoplastic antibodies:** anti-Hu, anti-Ma, anti-Yo, anti-VGKC.
Imaging:
- MRI with and without contrast; FLAIR and DWI, and ADC.
- CT chest, abdomen, pelvis.
- PET scanning (FDG, PiB etc.)

CSF:
- Protein, glucose,
- IgG, OCBs,
- cell count and differential Cultures,
- viral studies,
- protein 14-3-3; amyloid β 1-42, total and phosphorylated tau

Standard EEG

To summarize:
- RPD is dementia which develop after 12 months from the appearance of first cognitive symptom.
- RPD represent one of the most challenging disease facing the neurologist.
- Diagnostic evaluation is typically more comprehensive than with chronic neurodegenerative conditions.
To summarize:

- The broad differential requires the clinician to take a standardized method to any patient presenting with RPD.
- The diagnose of potentially treatable conditions such as HE, anti-voltage-gated encephalopathy, and paraneoplastic LE and distinguish these conditions from diseases such as CJD, which carry a more grave prognosis.

Thank You