**Study of the Spectrum of Treatable Dementias: Insights from a Large South Asian Cohort (TREAT-Dem Study)**

**TREAT-Dem Study**

**Supplementary article**

***Testing Methods:***

1. Autoimmune Antibody Profiling: Antibodies to N-methyl-D-aspartate (NMDA) receptor, voltage-gated potassium channel (VGKC), leucine-rich glioma-inactivated 1 (LGI-1), contactin-associated protein-like 2 (CASPR2), gamma-aminobutyric acid (GABA) receptor A/B were detected using a cell-based immunoassay with transfected cell lines. This method allowed for qualitative/semi-quantitative determination of human IgG antibodies in serum/plasma/CSF at a 1:10 dilution.

2. ANA Profile: Antibodies against nRNP-Sm, Sm, SS-A, Ro-52, SS-B, Scl70, PM-Scl 100, Jo-1, CENP B, PCNA, dsDNA, Nucleosomes, Histones, Ribosomal P Protein, and AMA M2 were tested using indirect immunofluorescence on serum at a 1:10 dilution.

3. ANCA Testing: P-ANCA and C-ANCA were tested using indirect immunofluorescence on serum at a 1:10 dilution.

4. Anti-Thyroid Peroxidase (Anti-TPO) and Anti-Thyroglobulin (Anti-Tg): Anti-TPO and Anti-Tg levels were measured using enzyme-linked immunosorbent assay (ELISA) for quantitative determination of antibodies in serum/plasma.

5. EEG Recording: A 40-60 minute EEG recording was conducted with adequate sleep and awake records using a 20-channel standard montage.

6. The MRI Brain protocol encompassed high-quality three-plane imaging (sagittal, coronal, and axial) with the following sequences: T1-weighted imaging (T1), T2-weighted imaging (T2), Fluid-attenuated inversion recovery (FLAIR), and Diffusion-weighted imaging (DWI).

**Table 1: Red Flags for Potentially Reversible Causes in Dementia: Binary Logistic Regression Analysis**

|  |  |  |  |
| --- | --- | --- | --- |
| **Factor** | **Odds ratio (OR)** | **CI (95%)** | **P-value** |
|  |  | **Lower limit** | **Upper limit** |  |
| Young age (<45 years) at onset | 2.35 | 1.66 | 3.31 | <0.001 |
| Fluctuations | 3.73 | 2.44 | 5.72 | <0.001 |
| A rapid decline in cognition | 3.02 | 2.16 | 4.21 | <0.001 |
| High-risk exposure | 11.76 | 1.22 | 113.41 | <0.001 |
| High-risk behaviour | 35.88 | 4.53 | 284.08 | <0.001 |
| NPA incongruent with history | 35.15 | 23.92 | 51.66 | <0.001 |
| Abnormal GPE | 8.79 | 3.04 | 25.47 | <0.001 |
| Unexplained neurological examination | 13.82 | 7.64 | 25.03 | <0.001 |
| ≥1 Red flag | 5.94 | 4.65 | 7.59 | <0.001 |
| ≥2 Red flags | 20.69 | 13.19 | 32.46 | <0.001 |
| ≥3 Red flags | 25.14 | 13.07 | 43.38 | <0.001 |

NPA: Neuropsychological assessment; GPE: General physical examination; CI: Confidence interval

**Case vignettes:**

1. A 69-year-old gentleman with no known comorbidities presented with forgetfulness over 2 years, money handling difficulties over 1.5 years, and wayfinding difficulty over 1 year, along with irritability over 8-9 months. On detailed enquiry, he was found to have deficits in perceptual motor, language, and memory, as well as complex attention domains, affecting his activities of daily living. Examination revealed hyperpigmented knuckles and absent ankle jerk, along with impaired vibration sensation. Cognitive assessment showed deficits in multiple domains, with an MMSE score of 20/30 and an ACE III (Hindi) score of 57/100 (Attention: 13/18, Memory: 4/26, Fluency: 5/14, Language: 24/26, visuo-spatial: 11/16). A possibility of early-onset Alzheimer's disease was considered, but due to the rapid unexplained decline in function and abnormal general or systemic physical examination, a possibility of other treatable etiologies like nutritional deficiencies was also considered. He consumes a vegetarian diet with a low intake of milk and dairy products. Investigations revealed low serum Vitamin B12 (160 pg/mL) and high serum homocysteine (22 umol/L) levels, consistent with a diagnosis of B12 deficiency. He was treated with intramuscular hydroxocobalamin, resulting in a subjective improvement of 70-80% and an objective improvement in MMSE from 21/30 to 25/30 over 4 months.

2. A 72-year-old retired assistant postmaster presented with memory disturbances for 3 years, irritability for 3 years, difficulty walking for 2.5 years, and urinary disturbances for 2 years. He experienced memory lapses such as forgetting items on a grocery list, parts of conversations, and messages to convey to his wife. Activities of daily living were affected. He had a history of hypertension and type 2 diabetes for 3 years and weakness of the right upper and lower limbs with atrophy since childhood, possibly due to childhood poliomyelitis. Examination revealed mild hypophonia, broken pursuits, hypometric saccades, mild bradykinesia, bilateral plantar flexors, start hesitation in gait, festinating gait, dragging of the right foot, turning with a pause and multiple steps, freezing, mildly stooped posture, and grade 1 postural instability. Cognitive assessment showed an MMSE score of 25/30, with deficits in orientation to time, registration, calculation, and recall. He exhibited deficits in complex attention, executive function, and learning and memory domains. A possibility of vascular cognitive impairment was considered, but due to the rapid unexplained decline in function and unexplained findings on the neurological examination, normal pressure hydrocephalus (NPH) was also suspected. MRI brain with CSF flow studies suggested NPH, and the CSF tap test was positive. After shunting, he showed subjective improvement of 70-80% and an objective improvement in MMSE from 25/30 to 28/30 over 3 months.

3. A 62-year-old male, a chartered accountant working as a financial consultant, presented with forgetfulness for 1.5 years and excessive daytime sleepiness for 2-3 years. He had difficulty remembering names but could describe the person, and he struggled with filling forms and cheques, sometimes forgetting to write the amount. He also experienced irritability, anger over small things, and loss of interest in daily activities, affecting his activities of daily living. He had a history of hypertension for 20 years, well-controlled with treatment, and was not known to be diabetic or have thyroid disorder. Physical examination was unremarkable, with a BMI of 30.8 kg/m². He had multiple episodes of daytime dozing, snoring, and early morning tiredness. Epworth Sleepiness Scale (ESS) was 13. Cognitive assessment showed an MMSE score of 30/30 but impaired delayed recall on the Kolkata verbal learning test (KVLT). Motor, sensory, and cerebellar examinations were unremarkable. Possibilities considered included non-specific cognitive decline with a secondary cause, given his rapid unexplained decline in function at a younger age than expected, and abnormal general or systemic physical examination findings. MRI brain was normal, but PSG showed severe obstructive sleep apnea with an Apnea-Hypopnea Index of 47.3. He was initiated on daily continuous positive airway pressure (CPAP) therapy and at 6 months follow-up reported a 65% subjective improvement in cognition based on ADLs, with enhanced name recall and reduced object misplacement, along with an improvement in ESS (13 to 3) and a stable MMSE at 30/30.

4. A 65-year-old professor of surgery presented with behavioral disturbances for 1 year, including apathy, sadness, and irritability, along with forgetfulness and inattentiveness for 6 months, and insidious onset of being disorganized. He had a history of lack of interest, anger outbursts, perseveration, insomnia, and delusions progressing over 5 months, with disinhibition, overfamiliarity, and delusions for 2 months. Referral diagnosis was behavioral variant frontotemporal dementia (bv-FTD). He had episodic depression twice, fluctuations in cognition, and no visual or auditory hallucinations, family history, or comorbidities. He was on Memantine and Fluoxetine but showed no improvement after 2-3 months. On examination, MMSE was 29/30, and ACE III score was 64/100 (Attention: 11/18, Memory: 11/16, Fluency: 5/12, Language: 25/26, Visuospatial: 12/16). He had no apraxia, agnosia, pyramidal, or extrapyramidal signs, and primitive reflexes were absent. MRI brain was unremarkable, and LP-CSF showed no cells, protein 27.4 mg/dL, glucose 65 mg/dL (GRBS 120), and strongly positive Serum GAD. He was treated with IVMP for 5 days/month for 6 months, followed by maintenance immunomodulators with Mycophenolate mofetil. Follow-up after 6 months showed subjective improvement of 20-30% in interaction, behavior, and memory, with an objective improvement in cognitive scores from ACE score 64 to 98.

5. A 37-year-old lady, an English teacher, presented with forgetfulness and a generalized sense of loss of energy for 6-7 months. She often misplaced objects, forgot recent events, and couldn't recall childhood or school memories. She frequently responded with "I don't know" and turned toward her mother when asked questions, affecting her activities of daily living. Detailed history revealed family disputes, stressed interpersonal relationships, and work-related stress. MMSE was 23/30, with deficits in recall and orientation. Motor, sensory, and cerebellar examinations were unremarkable. Cognitive domain assessment indicated deficits in learning and memory. Possibilities considered included young-onset dementia with a background history of multiple stressors, supported by incongruent neurocognitive testing, rapid unexplained decline in function, and younger-than-expected age at symptom onset. Laboratory investigations showed normal routine investigation including B12 and homocysteine levels and negative autoimmune and paraneoplastic panels. Clinically diagnosed as moderate depression, she was treated with Mirtazepine along with counseling sessions. Follow-up after 6 months showed subjective improvement of 50-60% and objective improvement in MMSE (23 to 29) with improved orientation, registration, attention, calculation, recall, language skills, and overall cognitive function.

6. A 63-year-old male, a retired judge of the high court, presented with forgetfulness and behavioral changes for 2 years. He frequently misplaced objects, missed appointments, and exhibited loss of interest in household activities, withdrawal, decreased interest in children, and an inability to understand people's emotions, including recognizing sadness in facial expressions. He also displayed inappropriate behaviors in certain situations. He self-medicated or overmedicated with multiple allopathic and indigenous medicinal substances for erectile dysfunction and sexual drive, occasionally using amitriptyline and diphenhydramine. Examination revealed an MMSE score of 28/30, with deficits in attention and calculation. Motor, sensory, and cerebellar examinations were unremarkable. Cognitive domain assessment indicated deficits in social cognition and complex attention. Possibilities considered included degenerative dementia with a non-specific phenotype, possibly evolving bvFTD. Atypical points included a rapid unexplained decline in function, younger than expected age at symptom onset, and a history of high-risk behaviors in the form of self-medications and medication overuse. MRI brain showed generalized cerebral atrophy, and routine investigations including B12, ANA, ANCA, paraneoplastic panel, and TPO ab were unremarkable. All over-the-counter and non-essential medications were stopped. Follow-up after 6 months showed subjective improvement of 60-70% and objective improvement in MMSE from 28 to 30.

7. A 36-year-old male presented with headaches for 9 months, forgetfulness for 6 months, and multiple episodes of convulsions for 5 months. He also experienced misplacing objects, irritability, loss of interest in daily activities, and confabulation, impacting his activities of daily living. He was not known to have diabetes, hypertension, or thyroid disorder but consumed alcohol 2-3 times a week and was a smoker. Examination revealed a low MMSE score of 18, with UMN facial palsy, mild abduction restriction in eye movements, bilaterally equal and reactive pupils, and exaggerated reflexes in the left upper and lower limbs, with extensor plantar response on the left. Power was 5/5 in the upper limbs and 3-4/5 in the lower limbs. Sensory system examination and coordination were apparently normal. Cognitive domain assessment indicated deficits in complex attention. Possibilities considered included raised intracranial tension syndrome, with atypical features such as rapid unexplained decline in function, acute or chronic high-risk exposures, and younger-than-expected age at symptom onset. MRI revealed deep cerebral venous thrombosis of the internal cerebral vein leading to bilateral thalamic infarcts. He was started on anticoagulation and anti-epileptic therapy. Follow-up after 8 months showed subjective improvement of approximately 80% in cognition based on ADLs, with improved ability to recall names promptly and very infrequent misplacement of objects. Objective improvement was noted with an MMSE score of 26.

8. A 58-year-old male physician from Kerala presented with behavioral symptoms persisting for 9 months and memory disturbances for 6 months. He had a history of obsessive-compulsive disorder (OCD) characterized by handwashing multiple times a day for the past 4-5 years, which had worsened over the last year. He also exhibited apathy, anxiety, social inappropriateness, reduced social interaction, and social withdrawal. He had a history of sweet craving and mild forgetfulness, occasionally becoming irritated over small issues. Examination revealed an MMSE score of 26/30, with deficits in recall and attention. Motor, sensory, and cerebellar examinations were unremarkable. Cognitive assessment showed deficits in social cognition and language. Differential diagnoses included behavioral variant frontotemporal dementia (bvFTD), but atypical points such as rapid unexplained decline in function and younger than expected age at symptom onset raised concerns. MRI brain showed bilateral fronto-temporal atrophy, and LP-CSF was unremarkable. Serum autoimmune panels were negative except for Anti-TPO Ab (>1300), suggesting a diagnosis of FTD with Hashimoto encephalopathy. He was treated with pulse methylprednisolone followed by monthly IVMP pulses. Follow-up at 6 months showed subjective improvement of approximately 60-70% based on ADLs, with increased social interaction, talkativeness, reduced obsession, and increased interest in family matters. Objective improvement was noted in MMSE, which increased to 28/30 (losing one point each in orientation and recall).

9. An 82-year-old lady, a homemaker, presented with behavioural changes over the past year, including way-finding difficulty, inability to recognize family members' faces, dressing difficulties, and forgetfulness for the last 6 months. She also exhibited irritability, anger outbursts, and decreased interest in family chores. Additionally, she had unconcerned urinary and fecal incontinence for 3 months. Examination revealed deficits in attention, memory, fluency, language, and visuospatial skills on the ACE-III illiterate version. Motor, sensory, and cerebellar examinations were unremarkable. All cognitive domains were involved, and an atypical point was noted for the rapid unexplained decline in function. Neuroimaging showed a right temporal space-occupying lesion (SOL), for which she underwent surgery. At 6-month follow-up, she showed mild improvement in symptoms, with an increase in ACE score from 65 to 72.