Look for the “Treatables” among dementias: It is lifesaving: An experience from a tertiary care center in India in the past 5 years

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ABSTRACT

Context: The aim is to awaken our colleagues to these reversible conditions. These are live saving if understood properly are life saving for patients. That is the purpose of this article and discussed in introduction. Aim: The aim of this study is to identify possible treatable causes in patients who present with progressive cognitive decline. These patients can be identified only by high degree of suspicion, thorough clinical examination and appropriate choosing of case-based investigations. This will be highly rewarding to the patients, their family, and to the treating physician. In this article, we are sharing our experience with the treatable dementias identified which were masquerading as degenerative. Settings and Design: Retrospective study. Subjects and Methods: Retrospective study of patients seen by the authors in the past 5 years who had all the mandatory recommended investigation done was included. Patients who qualified for pseudo-dementia and small vessel disease were not included in the analysis. Statistical Analysis Used: Basic statistical elements only were used as cases in each category are small. Results: Of 1105 patients, 92 had confirmed reversible cause. Among the treatable group immune-mediated dementia formed the largest and constituted about 45.6% followed by infections 19.5%, nutritional 15.2%, and rest were by rare conditions such as Whipple’s disease, cerebrotendinous xanthomatosis, mitochondrial disorders, primary demyelination, central nervous system (CNS) lymphoma, surgical conditions such as normal pressure hydrocephalus and subdural hematoma. Conclusion: About 12.1% percentage of patients with memory complaint has a reversible cause which when detected early, the quality of life of both the patient and caregiver are significantly improved. Apart from protocol-based categorization of the patients, individualized thorough clinical examinations are mandatory to identify these patients.

Key words: Dementia, detailed clinical evaluation, reversible causes

INTRODUCTION

Dementing illnesses are of great concern today with an increasing number of people presenting with memory complaint. In spite of continued research, results are not rewarding with reference to the degenerative dementias.\(^{[1]}\)

However, a proportion of these persons suffer from treatable dementias and every patient presenting with memory complaint should be evaluated for the same. Regular use of rating scales and neuropsychological testing will

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confirm memory complaint, but only a detailed history and thorough clinical evaluation will bring out the clinical clues regarding treatable dementias, confirming the significance of direct, detailed bed side assessment of every patient.\[2\] Dementia incidence is estimated to be about 5% in patients above 65 years and 20% in patients above 80 years. The frequency of reversible causes reported is as high as 23%.\[1,5\] The term reversible dementia was introduced in 1980 by the National institute of aging. The article “Fatal to reversible dementias” is a highly sensitizing article in this regard, which highlights the need to look at degeneration mimics.\[6\] Autoimmune encephalitis can closely mimic primary mental illness, degenerative dementia, and also Creutzfeldt Jakob disease (CJD) clinically as well as by other tests like electroencephalogram (EEG), but by careful evaluation based on clinical suspicion can be easily distinguished\[7\] [Table 1]. In our observation, we found that unexplained Panic, Catastonia, Excessive sleep changes, and delirium are features that help differentiate immune-mediated encephalopathy from degenerative dementias.\[8,10\] The next group of treatable causes are infections such as progressive multifocal leukoencephalopathy, human immunodeficiency virus (HIV)-associated dementia, neurosyphilis, Whipple's disease, neurocysticercosis (NCC), chronic bacterial infections,\[9,10\] neumetabolic diseases like mitochondrial disorders, Hashimoto’s encephalopathy, chronic encephalopathy due to renal, hepatic diseases, Wernicke’s encephalopathy, prolonged delirium, pseudo dementias, and chronic hyponatremia. Vascular causes include small vessel disease,\[11\] vasculitis, CADASIL, and toxic and metabolic disorders. Other causes are tumors of the central nervous system (CNS), normal pressure hydrocephalous (NPH) and systemic tumors with paraneoplastic manifestations. Indian studies show infections such as HIV, tuberculosis (TB), NCC, syphilis as important causes.\[12\] Treatable causes were more in patients under the age of 65 years and degenerative conditions above 65 years of age.

The recommended investigations apart from history and neuropsychological assessment are routine blood and urine, electrocardiogram, EEG, lumbar puncture, screening for infections, vasculitis, autoimmune and paraneoplastic conditions, imaging and brain biopsy if needed. The conditions which qualify for dementia at one time but improve or stabilize during longitudinal follow-up are the classical conditions included in the treatable category. Some useful bedside markers are the presence of skin changes such as ichthyosis, vitiligo, punched out ulcers, knuckle pigmentation, velvety skin, and raindrop pigmentation pointing to specific conditions and also nail changes of lead and arsenic poisoning.\[13\] History of hypophysitis points to probable sarcoïd, IGG4-associated encephalopathy, hystiocytosis, and TB. Patients should be evaluated for clinical features of endocrine disease such as hypothyroidism, hypopituitarism, and Addison’s disease. Tendon Xanthoma points to specific conditions like cerebrotendinous xanthomatosis (CTX) and joint involvement to SLE (systemic lupus erythematosus). History of chronic diarrhea is clue to coeliac disease, CTX, Mitochondrial neurogastrointestinal encephalopathy syndrome (MNGIE), malabsorption syndromes, and Whipple’s disease.

**SUBJECTS AND METHODS**

This is a retrospective study of patients with memory complaints seen in the past 5 years. Those patients with reversible dementia were evaluated for age, gender, type of dementia, and course of illness. Those patients who had all the mandatory workup needed for the patients with memory complaint which consists of Hindi Mental status Examination, Geriatric depression scale, everyday abilities Scale for India, Hachinskis ischemic score, blood levels of Vitamin B12, thyroid function test, liver function tests, renal function test, lipid profile, HIV, venereal disease research laboratory (VDRL), magnetic resonance imaging (MRI), EEG, and case-based tests as per indication in individual cases. Those who qualified for depression induced pseudo dementia, vascular cognitive decline due to small vessel disease were not included. Those patients who had qualified for reversible causes of memory impairment were taken for the detailed assessment of the diagnosis, treatment, and follow-up. All patients or care givers have agreed in writing at the time of admission for the use of their data for teaching purpose and other academic use. However, as it is retrospective study, no special consent could be obtained.\[1\]

\[Consent taken from all patients for utilizing their data for scientific purpose but not taken stating this particular paper.\]

| Table 1: Clinical features of Creutzfeldt Jakob disease and autoimmune encephalitis |
|-----------------|------------------|------------------|
| Parameters: Things to note | CJD | Autoimmune encephalitis |
| **Etiology** | Prion (proteinaceous infective substance) | Auto antibody |
| **Age group affected** | 5th decade | Any age |
| **Seizures** | Present | Present, fasciobrachial dystonic seizures are characteristic |
| **Myoclonus: Present/absent** | Classical 1 s | Nonperiodic myoclonus |
| **Important clinical features** | Rapidly progressive dementia with delirium, extrapyramidal features, blindness, ataxia, myoclonus | Rapidly progressive dementia, panic, sleepiness, catatonia, seizures |
| **EEG findings** | 1 s spikes, sharp waves, midpositive triphasic waves | Delta brush, nonperiodic sharp waves, spike and waves, slow waves |
| **MRI findings** | Cortical ribboning, pulvinar sign, inverted hockey stick sign (well appreciated in diffusion images and can be seen in T2-weighted images) | Medial temporal, insular, cingulum hippocampus, brainstem, cerebellum and white matter region hyper intensities |
| **Prognosis** | Fatal | Reversible is diagnosed in time |

CJD: Creutzfeldt Jakob disease, EEG: Electro encephalography, MRI: Magnetic resonance imaging
RESULTS

Total number of patients with dementia seen in the last 5 years by the authors is 1105. There were 735 males and 370 females [Figure 1]. The distribution of various diseases is as follows: 206 mixed dementia, 214-vascular dementia, 200 probable AD, 207 probable frontotemporal dementia (FTD), 17 Probable CJD, 69 Unclassified, 92 are Reversible [Figure 2]. Reversible dementias formed 12.1% of the total cases. Of these 92 patients who had reversible causes, 50 patients were referred to us with the diagnosis as psychiatric illness, 22 as degenerative dementias, 3 with suspected surgical causes, 7 as infection cases, and 10 as rapidly progressive dementia of unknown cause. After the completion of workup in our center, the pattern of disease among the identified 92 cases of reversible dementia is as follows: Autoimmune due to NMDA associated encephalitis (23), VGKC (11), paraneoplastic (3), Seronegative immune mediated (4), HIV + VGKC (1), systemic malignancy (2), Nutritional due to B12 deficiency (13) Pellagra (1), Demyelination (1), Chronic sub-dural hematoma ( SDH) (3) NPH (3), Infections (18), Mitochondrial due to MNGIE (1), MERRF (1), MELAS (5) and Endocrine (2) [Figure 3]. Duration of illness from onset of symptom to presentation to the hospital varied from 4 months to 3 years. Mean duration of illness before diagnosis was 16 months with range from 4 to 36 months. Brain biopsy was done in two patients which showed B- cell lymphoma in one and Cyto megalovirus (CMV) infection in the other [Figures 4 and 5]. All of them were less than 60 years of age. Time taken for confirmation of diagnosis was as early as 2 months in one patient and as late as 6 years in other patient.

DISCUSSION

Autoimmune encephalitis

It forms a very important group in this category. The Core symptoms of autoimmune encephalitis resemble mental illness, prion disease as well as dementia. The criteria for autoimmune encephalitis diagnosis are as follows: Sub-acute onset with progression of <3 months, working memory deficits, altered mental status, or psychiatric symptoms and at least one of the following like new focal CNS findings, unexplained seizure disorder, cerebrospinal fluid (CSF) pleocytosis, MRI features suggestive of encephalitis, and reasonable exclusion of alternative causes.[14,15] EEG changes help to establish organicity.[16,17] In this study, NMDA, VGKC, paraneoplastic syndromes were identified as causes of autoimmune encephalitis. All patients diagnosed, received pulse of methylprednisolone 5 g, plasmapharesis monthly for at least for 6 months, and interval therapy with either azathioprine or mycophenolate. Three patients received intravenous immunoglobulins.

One patient expired after 3 years of remission, following surgery for fracture hip and he developed super refractory
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seizures [Videos 1 and 2]. Others are in varying phases of improvement though complete normality was not seen in most patients at the end of 1 year. Mortality is 1.08% and morbidity could not be assessed in the NMDA group which constituted children. The others did not return to the pre-morbid functional status to their complete satisfaction except one patient who improved completely (1.08%). Two patients were seronegative to start with but clinical evidence of vasculitis was present, during the course of illness developed seropositivity for SLE and Sjogren’s. Vitamin B12 deficiency formed the major nutritional cause and features of Pellagra were present in one patient. Patients with hypothyroidism showed good recovery. Patient with mitochondrial disorders showed partial improvement with lifestyle change and by treatment with mitochondrial cocktail. Late-onset demyelination was seen in one patient presenting with cognitive symptoms. Among the surgical causes, outcome was good in patients with SDH.

Whipple’s disease

Whipple’s disease is uncommon in our country. It is caused by Gram- positive bacillus Tropheryma whipplei. CNS is affected in 20%–40% of patients. The features seen are headache, eye movement disorder, oculofacial-skeletal myorhythmia, dementia, and myoclonus. Oculomasticatory myorhythmia is pathognomonic and in addition, they can have other involuntary movements, Parkinsonism features, epilepsy, cerebellar ataxia, ophthalmoplegia, vertical gaze palsy, sleep changes, pigmentation changes, nodules, vesicles resembling dermatitis herpetiformis, decreased or altered appetite due to hypothalamic involvement, meningitis, and cortical blindness.

A 63-year-old male was admitted with a history of bouts of abdominal colic, poor appetite, loose stools, loss of about 7 kg weight in 1 year, fatigue, and headache. This was followed by slowness of gait, falls, weakness of the left side of the body, loss of balance, slurring of speech, involuntary movement of eye, face, limbs, and swallowing difficulty in the form of coughing while swallowing. He was apathetic, forgetfulness for recent events, and had non-stereotyped formed visual hallucinations. Patient was steadily deteriorating his Hindi mental status examination (HMSE) score was 19. The patient had involuntary closing and opening of each eye in disconjugate arrhythmic manner, eyebrow lifting movements, dyskinetic movements of upper lips, cheek, as well as mild elevation of shoulders, and twisting of trunk. His ocular findings were skew deviation of the eyes with saccadic initiation defect, broken saccades, slow vertical saccades, and multiple saccadic oscillations. In addition, forwardstoop, swaying while walking, Truncal imbalance while sitting, finger-nose incoordination, and completely illegible effortless speech, poor lip seal, slowness of tongue movements; he had itchy skin lesions over scalp, cheek, nose, and chin. Duodenal biopsy showed lamina propria showing focal lymphoplasmacytic cell collections and few histiocytes. Grams stain, Periodic acid–Schiff, and Crocott’s Methenamine silver did not reveal any bacilli.

MRI: T1 and T2 images showed multiple areas of signal changes in the left middle cerebellar peduncle, midbrain, cerebellum, with diffuse cerebral and cerebellar atrophy; creatine peak was seen in the area of signal change. DOPA uptake scan showed poor uptake in putamen. The patient was treated with injection ceftriaxone 2 g twice a day for

Figure 5: (a) Magnetic resonance imaging with fluid-attenuated inversion recovery showing symmetrical white matter changes with nodularity. (b) Striatal bundles sample showing white matter fragments of neuroparenchyma infiltrated by atypical lymphoid cells. (c) High magnification showing neoplastic lymphoid cells and mitosis (arrows). (d) Angiocentric arrangement of tumor cells (circled). (e) Tumor cells are positive for leukocyte common antigen, CD20 (B-cell marker). Occasional reactive intermingled lymphocytes are CD3 (T cell marker positive). MIB-1 labeling is high (proliferative marker), the stroma shows reactive gliosis (glial fibrillary acidic protein).
2 weeks. Trimethoprim-sulfamethoxazole twice a day, doxycycline 100 mg a day and symptomatic measures. At 3 month follow-up, patient had improvement in speech, swallowing and walking, skin, and gastrointestinal features. One and half years later, patient passed away due to pneumonia.

**B-cell lymphoma**

A 50-year-old male presented with progressive cognitive decline of 6 months duration. He had headache and later showed bilateral pyramidal signs. His MRI revealed diffuse white matter changes and nodular areas. Histopathology revealed whitematter fragment of neuroparenchyma infiltrated by atypical lymphoid cells. High magnification showed neoplastic lymphoid cells and mitosis. Angiocentric arrangement of tumor cells was also seen. Tumor cells were positive for Leukocyte common antigen – which is a common lymphocyte marker), CD20 (B-cell marker) consistent with B-cell lymphoma. Occasional reactive intermingled lymphocytes were CD3 (T-cell marker) positive. MIB-1 labeling is high (proliferative marker). The stroma showed reactive gliosis on glial fibrillary acidic protein stain [Figure 4]. The most common malignancies masquerading as rapidly progressive dementia are primary CNS lymphoma and intravascular large B-cell lymphoma, both rare and difficult to diagnose without brain biopsy. Other mitochondrial diseases present with following clues: Stroke like episodes in a non-territorial fashion with encephalopathy, clues-like short stature, midline lipomas, RP (Retinits Pigmentosa), multiaxial involvement and fever induced exacerbations cross territorial diffusion restricting lesions give the clue to diagnosis.

**Mitochondrial encephalopathy**

MNGIE is an autosomal recessive mitochondrial disease. It presents with polyneuropathy, ophthalmoplegia, leukoencephalopathy, and starts in childhood as unexplained intestinal symptoms, and slowly progressive cognitive decline with remissions and exacerbations. Our patient presented to us at the age of 12 with abdominal pain, diarrhea, and rapid deterioration in cognitive functions. She was investigated for coeliac disease which was noncontributory. MRI showed diffuse white matter changes and genetic evaluation confirmed MNGIE. She showed improvement with mitochondrial cocktail. Later, she was lost for follow-up for several years. She was being treated on several occasions as refractory GIT infection from other centers. She deteriorated severely in her cognitive functions, Motor functions involving both upper motor neuron and lower motor neuron in the form of extensor plantar responses and peripheral neuropathy was noticed. She was being treated with mitochondrial cocktail infusion of Vitamin B1 and symptomatic measures and prognosis was explained to family.

**Paraneoplastic dementias**

Paraneoplastic cognitive dysfunction can be due to limbic encephalitis, Nutritional causes and also due to unknown mechanisms. In our group, we found two patients presenting with myeloneuropathy, Knuckle pigmentation, and progressive cognitive decline. Investigation for appetite loss and vomiting revealed Linitis Plastica in one patient.

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*Figure 6:* Patient having dementia with peripheral neuropathy, modified Gomaris Trichrome stain showing Ragged Red Fibers, leukoencephalopathy in magnetic resonance imaging and confirmed genetically.
and adenocarcinoma stomach in another patient. Cognitive functions improved with Vitamin B12 replacement. A 70-year-old male presented with progressive apathy and recent memory impairment. He in addition had loss of weight about 14 kg in 6 months and had skin tags in both feet. Evaluation showed advanced malignant thymoma, confirming paraneoplastic dementia.[10] A 64-year-old male was diagnosed as progressive supranuclear palsy syndrome in view of pseudobulbar features, apathy, extrapyramidal, and pyramidal signs. However, he had significant weight loss, palatal palsy on the left side and was smoker from the age of twelve. All investigation including whole-body positron emission tomography (PET) was normal. However, anti-Ri antibody was positive, and therefore patient was treated with large volume plasmapheresis.

Patient symptomatically improved and therefore plasmapheresis was repeated as and when patient’s neurological features worsened. Two years after the onset of illness, reevaluation with PET scan showed angiosarcomatous deposit in scalp and primary remained undetected [Figure 7].[20,21]

**Trombone tongue and neurosyphilis**

Neurosyphilis commonly presents as asymptomatic, meningeal, vascular, and parenchymatous and mixed forms. It is a well-known imitator from time immemorial and these patients get labeled as psychosis which gave the condition the name the general paralysis of the insane. The points which are clues are persistent dull headache, cutaneous, and general features of syphilis such as Rhagades, leukomelanoderma, pigmented papery scar, lymphadenopathy, Argyl and Robertson Pupil. A typical dyskinesia of the lips and lower facial muscles called as “candy sign.” Orofacial chorea, trombone tremor of the tongue, Grandiose delusion, mania cellular CSF and un-patterned cognitive decline with dominant frontal lobe, and subcortical feature scan be seen.

Our patient was a female in late fourth decade who was being treated as BvFTD and was suffering from the lack of initiative, aggression, poor sleep, hallucinations, delusions, wandering behavior, and double incontinence and complete dependence for Activities for daily living (ADL) on family members. Clues for the diagnosis of neurosyphilis was onset with headache and tongue tremor [Video 3]. VDRL was 1:64 titer positive and TPHA was also positive. The patient was treated with Crystalline penicillin G 24 million units intravenously and developed seizures and encephalopathy while on treatment after 4 days. Then, she was treated with ceftriaxone and symptomatic measures. Two years after treatment, her tongue tremors reduced. She became continent and independent in her ADL. She started assisting her family members in house hold activities but continued to be cognitively impaired.[22-24] Other infections seen in this group are Toxoplasmosis, NCC as well as TB [Figure 8].

**Cerebrotendinous xanthomatosis**

CTX is a rare treatable inborn error of bile acid metabolism. Reported average duration of delay from onset of symptoms to diagnosis is about 16 years as per reports. Patients respond very well to treatment, if diagnosed before significant neurological damage had occurred. Short stature, tendon

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**Figure 7**: Patient 1 (a) with skin tags, (b) thymic tumor, (c) magnetic resonance imaging showing signal changes in the insular region, (d) patient 2 showing leather bottle stomach, (e) patient 3 showing angiosarcomatous deposit in the scalp
xanthomas, fractures can be identified by the systematic evaluation of the whole patient.\[^{25}\]

Our patient is a 40-year-old married woman, born out of consanguineous parents with poor scholastic performance compared to her siblings. At the age of 29 years, she underwent both medical and surgical treatment for her swelling over both tendo-achilles without any permanent cure. Later developed hypothyroid state, dysarthria, repeated falls which led to fractures of both bones of forearm, 1\(^{st}\) metatarsals, clavicle, and right femur [Figure 9]. This was followed by procedural memory problems in ADL, misplacing objects; not mingling with relatives; speaking very few words with low voice volume; unable to remember events which occurred few days ago; not interested in bathing, brushing, and dressing properly, aimless wandering, hoarding, excessive anger, and suspiciousness. At the age of 39, she was passing urine and stools in inappropriate places. With the onset of these symptoms, she was referred as a case of FTD to our center. Examination revealed a short-statured woman with haggard face, goiter, firm swellings over the both tendo-achilles, (about 7–10 cm). She had bilateral cataract and ataxia. HMSE was 18/31. Investigations revealed Vitamin D2 ergocalciferol: 1.27 ng/ml, Vitamin D3 cholecalciferol: 20.64 ng/ml, and total Vitamin D level: 21.9 ng/ml. Parathormone level was 19.7 pg/ml. Cholesterol levels include the following: Total cholesterol–221 mg/dl; high-density lipoprotein – 31.1 mg/dl; low-density lipoprotein (LDL)– 156 mg/dl; very LDL– 34 mg/dl; phosphorus – 4.6 mg/dl; calcium – 9.67 mg/dl; and homocysteine– 7.54 mmol/l. Cholestenol could not be done. EEG showed frontal slowwaves of theta range with a burst of asymmetrical, asynchrous, mid-positive, triphasic waves with anteroposterior gradient. Her MRI showed diffuse atrophy more pronounced over the frontal and temporal regions as well as cerebellar vermis. X-ray of her bones showed multiple malunited fractures with severe osteopenia. Neuropsychological evaluation showed frontotemporal dysfunction. She was treated with azodeoxycholic acid and at 1-year follow-up she is stable.

**Chronic cyto megalovirus encephalitis**

A 45-year-old male presented with sub-acute onset of behavioral problem in the form of withdrawn behavior, confusion, excessive sleepiness, and forgetfulness of 9 months duration. Imaging showed bulky temporal lobes and T2 hyperintensities, as the symptoms were slowly progressive, possibility of mass lesion was considered and biopsy was done. Brain Biopsy showed meningeal perivascular inflammation with microglial nodules which were positive for T cell and macrophage markers [Figure 10]. Neurophagia characterized by T lymphocytes attacking infected neurons was seen. CMV IgG and IgM were significantly elevated in serum. Patient was treated with antiviral agent but developed status epilepticus and succumbed 6 months later. Auto immune dementias causing false-positive elevation of Measles antibody is reported.\[^{26}\]

**Nutritional causes**

The most common cause in this group are related to Vitamin B12 deficiency who present with skin changes in the form of vitiligo, knuckle pigmentation, beefy tongue, peripheral neuropathy, frontal and temporal lobe dysfunction and myelopathy. Of 13 patients with Vitamin B12 deficiency induced dementia, 2 patients had evidenced of carcinoma stomach and 7 patients are positive for parietal cell antibody and the rest showed chronic gastritis. Myelopathy and Neuropathy was seen in 4 of the patients.

**Pellagra**

A 29-year-old male chronic alcoholic presented with rapidly progressive dementia with features of frontal and temporal

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**Figure 8:** (a) Magnetic resonance imaging showing features of toxoplasmosis, (b) starry sky of neurocysticercosis, (c) tuberculoma with meningeal enhancement

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lobe involvement. On examination, the classical velvety skin appearance of pellagra was seen with peripheral neuropathy. All patients’ cognitive symptoms improved with Vitamin supplementation over a period of 3 months [Figure 11].

Table 2 shows the general prevalence of the reversible causes.

CONCLUSION
In this study of patients seen by the team of authors, 12% of patients with cognitive complaint had a reversible cause.

Therefore, it is better to rule out reversible causes before concluding patients with memory complaints as suffering from irreversible causes. Detailed history and clinical examination greatly assists in clinching the diagnosis and aids in planning treatment. Protocol-based assessment helps to confirm the presence or absence of cognitive dysfunction. Mandatory recommended laboratory tests only exclude the conditions included in that category and therefore have to be redesigned. There is no substitute for the time spent at the bedside in history taking and complete examination of the patient.

Discussion on algorithm [Flow chart 1]
All patients who are found to have memory complaint on screening should be categorized as long duration when the onset is vague and usually several months. They are mostly degenerative. Short duration ones with a fairly well-defined onset are the patients who need to be analyses for treatable cause. If they have features of raised intracranial pressure they belong to space occupying lesions. If not look for features of other parts of nervous system involvement in addition to cortex which points to vascular, infective, traumatic, or autoimmune causes. If the disease is confined to cortex rapid presentation of degeneration is still a possibility in addition to metabolic, toxic, nutritional, and...
**Table 2: The prevalence and clinical features of the treatable cases in India**

| Type of irreversible dementia | Core symptoms | Clinical resemblance/clinical mimickers | Criteria for diagnosis | Usual presentation in our set up | Investigations | Treatment given | Prognosis | Remarks/other important findings |
|-------------------------------|---------------|----------------------------------------|------------------------|----------------------------------|---------------|-----------------|-----------|----------------------------------|
| Autoimmune encephalitis      | The core symptoms of autoimmune encephalitis resemble mental illness, prion disease as well as dementia | The criteria for autoimmune encephalitis diagnosis are as follows: Subacute onset with progression of <3 months, working memory deficits, altered mental status, or psychiatric symptoms and at least one of the following like new focal CNS findings, unexplained seizure disorder, CSF pleocytosis, MRI features suggestive of encephalitis and reasonable exclusion of alternative causes. EEG changes help to establish organicity | NMDA, VGKC, paraneoplastic syndromes were identified as causes of autoimmune encephalitis | EEG, MRI brain CSF analysis for infections and autoimmune panel Serum paraneoplastic panels | All patients diagnosed, received pulse of methylprednisolone 5 g, plasmapheresis monthly for at least for 6 months and interval therapy with either azathioprine or mycophenolate. Three patients received IVIG. None in this group received other immuno modulators | One patient expired after 3 years of remission, following surgery for fracture hip and he developed super refractory seizures [Video 1, 2]. Others are in varying phases of improvement though complete normality was not seen in most patients at the end of 1 year. Mortality is 1.08% and morbidity couldn't be assessed in the NMDA group which constituted children. The others didn't return to the premorbid functional status to their complete satisfaction except one patient who improved completely (1.08%). Two patients who were seronegative to start with though clinical evidence of vasculitis was present but during the course of illness developed seropositivity for SLE and Sjogren's syndrome. | Vitamin B12 deficiency formed the major nutritional cause and features of pellagra were present in one patient. Patients with hypothyroidism showed good recovery. Patient with mitochondrial disorders showed partial improvement with lifestyle change and by treatment with mitochondrial cocktail. Late onset demyelination was seen in one patient presenting with cognitive symptoms. Among the surgical causes, outcome was good in patients with SDH |
| Whipple's disease            | CNS is affected in 20%-40% of patients. The features seen are headache, eye movement disorder, oculocutaneous-skeletal myorhythmia, dementia and myoclonus. OMM is pathognomonic and in addition they can have other involuntary movements, parkinsonian features, epilepsy, cerebellar ataxia, ophthalmoplegia, vertical gaze palsy, sleep changes, pigmentary changes, nodules, vesicles resembling dermatitis herpetiformis, decreased or altered appetite due to hypothalamic involvement, meningitis and cortical blindness | Bouts of abdominal colic, poor appetite, loose stools, loss of about 7 kg weight in 1 year, fatigue, and headache slowness of gait, falls, weakness of the left side of the body, loss of balance, slurring of speech, involuntary movement of eye, face, limbs, and swallowing difficulty in the form of coughing while swallowing, aphathy, forgetfulness for recent events, and had nonsteriotype formed visual hallucinations | Duodenal biopsy showed lamina propria showing focal lymphoplasmacytic cell collections and few histiocytes. Gram-stain, PAS, and GMS did not reveal any bacilli MRI: T1 and T2 images showed multiple areas of signal changes in the left middle cerebellar peduncle, midbrain, cerebellum, with diffuse cerebral and cerebellar atrophy; creatine peak was seen in the area of signal change. DOPA uptake scan showed poor uptake in putamen | Injection ceftriaxone 2 g twice a day for 2 weeks. Trimethoprim-sulfamethoxazole twice a day, doxycycline 100 mg a day and symptomatic measures | Three months follow-up patient had improvement in speech, swallowing and walking, skin and gastrointestinal features. One and half years later patient passed away due to pneumonia |

*Contd...*
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|------------------------------|--------------|-----------------------------------------|------------------------|---------------------------------|--------------|---------------|-----------|----------------------------------|
| B cell lymphoma              | 50 year old male presented with progressive cognitive decline of 6 months duration. He had headache and later showed bilateral pyramidal signs | MRI revealed diffuse white matter changes and nodular areas. Histopathology revealed whitematter fragment of neuroparenchyma infiltrated by atypical lymphoid cells. High magnifications showed neoplastic lymphoid cells and mitosis. Angiocentric arrangement of tumor cells was also seen. Tumor cells were positive for LCA - which is a common lymphocyte marker, CD20 (B cell marker) consistent with B-cell lymphoma. Occasional reactive intermingled lymphocytes wereCD3 (T-cell marker) positive. MIB-1 labeling is high (proliferative marker). The stroma showed reactive gliosis on GFAP stain [Figure 4] | | | | | The commonest malignancies masquerading as rapidly progressive dementia are primary CNS lymphoma and intravascular large B-cell lymphoma, both rare and difficult to diagnose without brain biopsy. Thorough history and radiological features are important for diagnosis |
| MNGIE                        | 12 year aged patient with abdominal pain, diarrhea and rapid deterioration in cognitive functions. She was investigated for coeliac disease which was nonconnotutory. MRI showed diffuse white matter changes and genetic evaluation confirmed MNGIE | MRI brain showed diffuse white matter changes and genetic evaluation confirmed MNGIE | Mitochondrial cocktail, infusion of vitamin B1 and symptomatic measures | Mitochondrial diseases present with following clues: Stroke like episodes in a nonterritorial fashion with encephalopathy, clues like short stature, midline lipomas, RP, multisexual involvement and fever induced exacerbations cross territorial diffusion restricting lesions give the clue to diagnosis |
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|-----------------------------|---------------|-----------------------------------------|------------------------|----------------------------------|----------------|----------------|----------|----------------------------------|
| Paraneoplastic dementias    | Paraneoplastic cognitive dysfunction can be due to limbic encephalitis, nutritional causes and also due to unknown mechanisms | Two patients presenting with myeloneuropathy, Knuckle pigmentation and progressive cognitive decline A 70 year old male presented with progressive apathy and recent memory impairment. He in addition had loss of weight about 14 kg in 6 months and had skin tags in both feet. Evaluation showed advanced malignant thymoma, confirming paraneoplastic demential[10] A 64 year old male was diagnosed as PSP syndrome in view of pseudobulbar features, apathy, extrapyramidal and pyramidal signs. However, he had significant weight loss, palatal palsy on the left side and was smoker from the age of twelve | Investigation for appetite loss and vomiting revealed Linitis Plastica in one patient and adenocarcinoma stomach in another patient. Cognitive functions improved with Vitamin B12 replacement All investigation including whole body PET was normal. But anti-Ri antibody was positive 2 years after the onset of illness, reevaluation with PET scan showed Angiosarcomatous deposit in scalp and primary remained undetected[Figure 7][20,21] | Plasma pharesis |
| Trombone tongue and neurosyphilis | Neurosyphilis commonly presents as asymptomatic, meningeal, vascular and parenchymatous and mixed forms. It is a well-known imitator from time immemorial and these patients get labelled as psychosis which gave the condition the name GPI the (GPI) Persistent dull headache, cutaneous and general features of syphilis like Rhagades, leukomelanoderma, pigmented papery scar, lymphadenopathy, ARP. A typical dyskinesia of the lips and lower facial muscles called as “Candy sign.” | A female in late fourth decade who was being treated as BvFTD and was suffering from lack of initiative, aggression, poor sleep, hallucinations, delusions, wandering behaviour and double incontinence and complete dependence for ADL on family members. VDRL was 1:64 titer positive and TPHA was also positive | The patient was treated with Crystalline penicillin G 24 million units intravenously and developed seizures and encephalopathy while on treatment after 4 days. Then she was treated with ceftriaxone and symptomatic measures | Two years after treatment her tongue tremors reduced. She became continent and independent in her ADL. She started assisting her family members in house hold activities but continued to be cognitively impaired[22,23] |
### Table 2: Contd...

| Type of irreversible dementia | Core symptoms                                                                 | Clinical resemblance/clinical mimickers                                                                 | Criteria for diagnosis | Usual presentation in our set up                                                                 | Investigations                                                                 | Treatment given | Prognosis | Remarks/other important findings |
|-------------------------------|-------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|------------------------|--------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|----------------|-----------|----------------------------------|
| CTX                           | Orofacial chorea, trombone tremor of the tongue, Grandiose delusion, mania cellular CSF and un-patterned cognitive decline with dominant frontal lobe and subcortical features can be seen | Clues for the diagnosis of neurosyphilis was onset with headache and tongue tremor (video 3)           |                        |                                                                                                  | A 40-year-old married woman, born out of consanguineous parents with poor scholastic performance compared to her siblings. At the age of 29 years, she underwent both medical and surgical treatment for her swelling over both tendo-achilles without any permanent cure. Later developed hypothyroid state, dysarthria, repeated falls which led to fractures of both bones of forearm, first metatarsals, clavicle, and right femur [Figure 9]. | Investigations revealed: Vitamin D2 ergocalciferol: 1.27 ng/ml, Vitamin D3 cholecalciferol: 20.64 ng/ml, and total Vitamin D level: 21.9 ng/ml. Parathormone level was 19.7 pg/ml. Cholesterol levels include the following: Total cholesterol - 221 mg/dl; high-density lipoprotein - 31.1 mg/dl; LDL - 156 mg/dl; very LDL - 34 mg/dl; phosphorus - 4.6 mg/dl; calcium - 9.67 mg/dl, and homocysteine - 7.54 mmol/l. Cholesterol couldn't be done. EEG showed frontal slow waves of theta range with a burst of asymmetrical, asynchronous, mid-positive, triphasic waves with anteroposterior gradient. | She was treated with azoodeoxycholic acid | At 1 year follow she is stable |
| Type of irreversible dementia | Core symptoms | Clinical resemblance/ clinical mimickers | Criteria for diagnosis | Usual presentation in our set up | Investigations | Treatment given | Prognosis | Remarks/other important findings |
|------------------------------|--------------|----------------------------------------|------------------------|---------------------------------|--------------|-----------------|----------|-----------------------------|
| Chronic CMV encephalitis (CMV) | This was followed by procedural memory problems in ADL, misplacing objects; not mingling with relatives; speaking very few words with low voice volume; unable to remember events which occurred few days ago; not interested in bathing, brushing, and dressing properly; aimless wandering, hoarding, excessive anger, and suspiciousness. At the age of 39, she was passing urine and stools in inappropriate places. With the onset of these symptoms, she was referred as a case of FTD to our center | Her MRI showed diffuse atrophy more pronounced over the frontal and temporal regions as well as cerebellar vermis X-ray of her bones showed multiple malunited fractures with severe osteopenia. Neuropsychological evaluation showed frontotemporal dysfunction | Imaging showed bulky temporal lobes and T2 hyperintensities, as the symptoms were slowly progressive, possibility of mass lesion was considered and biopsy was done. Brain biopsy showed meningeal perivascular inflammation with microglial nodules which were positive for T cell and macrophage markers [Figure 10]. Neuronophagia characterized by T lymphocytes attacking infected neurons was seen. CMV IgG and IgM were significantly elevated in serum | Patient was treated with antiviral agent | Developed status epilepticus and succumbed 6 months later |
| Type of irreversible dementia | Core symptoms | Clinical resemblance/clinical mimickers | Criteria for diagnosis | Usual presentation in our set up | Investigations | Treatment given | Prognosis | Remarks/other important findings |
|------------------------------|---------------|-----------------------------------------|------------------------|-----------------------------|---------------|----------------|-----------|----------------------------------|
| Immune mediated dementias    | Group of conditions where dementia is due to immune dysregulation. This may be seronegative or seropositive, paraneoplastic or nonparaneoplastic | It affects young people and presents with new onset psychosis and delirium. Abnormalities of sleep, catatonia, seizures, myoclonus and multidomain cognitive decline are common clues | | We had a total of 23 patients with NMDA antibodies and 11 with VGKC antibodies |
| Nutritional causes           | Commonest cause in this group are related to Vitamin B12 deficiency who present with skin changes in the form of vitiligo, knuckle pigmentation, beefy tongue, peripheral neuropathy, frontal and temporal lobe dysfunction and myelopathy | | We had a total of 23 patients with NMDA antibodies and 11 with VGKC antibodies |
| Pelagra                      | 29 year old male chronic alcoholic presented with rapidly progressive dementia with features of frontal and temporal lobe involvement. On examination, the classical velvety skin appearance of pellagra was seen with peripheral neuropathy | | All patients cognitive symptoms improved with Vitamin supplementation over a period of 3 months [Figure 11] |

MNGIE: Mitochondrial neurogastrointestinal encephalopathy syndrome, CTX: Cerebrotendinous Xanthomatosis, CMV: Cytomegalovirus, CNS: Central nervous system, OMM: Oculomasticatory myorhythmia, GPI: General paralysis of the insane, ARP: Argyl Robertson Pupil, EEG: Electroencephalography, MRI: Magnetic resonance imaging, CSF: Cerebrospinal fluid, FTD: Frontotemporal dementia, PSP: Progressive supranuclear palsy, BvFTD: behavioral variant FTD, ADL: Activities for daily living, LCA: Leukocyte common antigen, LDL: Low-density lipoprotein, IVIGs: Intravenous Immunoglobulins, SLE: Systemic lupus erythematosus, SDH: Sub-Dural hematoma, RP: Retinitis Pigmentosa, NMDA: N-Methyl-D-aspartate antibody, VGKC: Voltage Gated potassium channel antibody, PAS: Periodic acid schiff, GMS: Grocott methenamine silver, PET: Positron emission tomography, VDRL: Venereal disease research laboratory, GFAP: Glial fibrillary acidic protein, TPHA: Trypanema pallidum haem agglutination test, DOPA: Dopamine, MIB: Molecular Imaging In Biology.
autoimmune causes. Features of hypophysitis are seen in TB, Sarcoid, IGG4-associated syndrome, histiocytosis, etc., New-onset psychosis strongly raises suspicion of SLE and autoimmune causes. Gastrointestinal symptoms are seen in CTX, Whipples disease, mitochondrial disease, celiac, and nutritional disorders. Skin, hair, nail features point to nutritional, toxic, endocrine, vasculitis causes. This algorithm will be an easy bedside reference tool for treating doctors.

This is only a descriptive study of our patients. Long-term outcomes, detailed treatment given are not discussed as most patients are in varying stages of treatment and could not be fully evaluated.

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Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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Flow chart 1: Quick bedside flowchart
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