Misdiagnosis leads to Iatrogenesis

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CASE VIGNETTE

A 71-year-old man was referred to the Memory clinic complaining of problems with his memory and general motor skills over a period of two years. He had progressive difficulty navigating his way around when travelling, recalling recent events, was misplacing things and often forgot conversations as well as names of people he had met. He had started having visual hallucinations at approximately the same time, often of well-formed images of people visiting his house. His family also reported episodes of reduced alertness and occasional slurring of speech. He had become more unsteady lately and thought that his balance was much worse than before although he had not had any falls. He also felt greater difficulty doing certain things like buttoning his clothes, putting in his dentures or lighting a cigarette. His sleep was generally good but he often sleep-talked and on occasions sleepwalked. His past history included hypertension, hypercholesterolaemia and spinal stenosis. He denied poor mood and had no other complaints aside from constipation.

He was seen by various doctors over the previous two years and had initially been diagnosed as having had a small stroke. He was then given a diagnosis of Mild Cognitive Disorder, and subsequently, early Alzheimer's disease with Behavioural and Psychological symptoms of Dementia. He had recently been further diagnosed with depression associated with an obsessive-compulsive disorder and had been started on Escitalopram as well as Risperidone. His family was keen to get a further opinion as he had become significantly more confused since then. Other medications included Atorvastatin, Aspirin and Amlodipine.

Family history was non-contributory. He was a retired public servant and was running a business with investments in China. He smoked half a packet of cigarettes daily, drank occasionally and was independent in self-care aside from occasionally needing help with buttons. He had a personal attendant who helped him keep track of appointments.

On physical examination, there was evidence of mild bradykinesia. He had mask-like facies. Tone was increased. There was no tremor. Power was normal as was sensation.

His blood tests were within normal parameters. A CT scan brain done two years ago at the onset of his hallucinations and repeated recently showed no abnormalities aside from a small Arterial-Venous malformation in the left temporal area. An MRI brain a year ago showed no new abnormalities. An EEG showed mild diffuse slow waves suggestive of mild diffuse cortical dysfunction. Mini mental state examination score when seen was 19/30 with orientation 7/10, attention 3/5 and recall 0/3. His copy pentagons and Clock Drawing Test (CDT) is shown in Figure 1. MMSE done two years ago was 26/30 with orientation 9/10 and attention 3/5. His copy pentagons then are shown in Figure 2.

What should be your next course of action?
A. Repeat his MRI brain
B. Get a neurosurgical opinion
C. Increase his dose of Escitalopram
D. Stop Risperidone
E. Start Madopar

DISCUSSION

Dementia with Lewy Bodies (DLB) is thought to be the second most common cause of neurodegenerative dementia, accounting for 10-22% of all cases of dementia. Prevalence increases with age and is estimated to be 0.7% for individuals over the age of 65 years. Onset is usually between 50-80 years with mean age of presentation around 75 years. It is more common in men and sporadic in most cases although familial cases of DLB have been reported, associated with triplication of α-synuclein gene.

The exact cause of DLB is unknown but involves the abnormal deposition of round, eosinophilic inclusions of α-synuclein protein in the nuclei of neurons, known as Lewy bodies. This relationship between cortical Lewy bodies and dementia was first described in 1961 by Okazaki. Other pathological findings include Lewy neurites which are degenerating neural processes which stain positive for ubiquitin and α-synuclein as well as amyloid plaques in up to 1/3 of cases. Neurofibrillary tangles are often sparse or absent. There is often spongiform change in the temporal cortex due to microvacuolation and neuronal loss greater in the frontal lobes, nuleus basilus of Maynert, substansia nigra and locus ceruleus.

Dementia, defined as progressive cognitive decline sufficient enough to interfere with activities of daily living, is essential for a diagnosis of DLB. Cognitive dysfunction in DLB is often characterised by early impairment in attention as well as executive and visuospatial dysfunction. Memory tends to be affected later in the course of the disease.

Core features of DLB include fluctuations in cognition with pronounced variations in attention and alertness, one or more cardinal features of Parkinsonism not due to other

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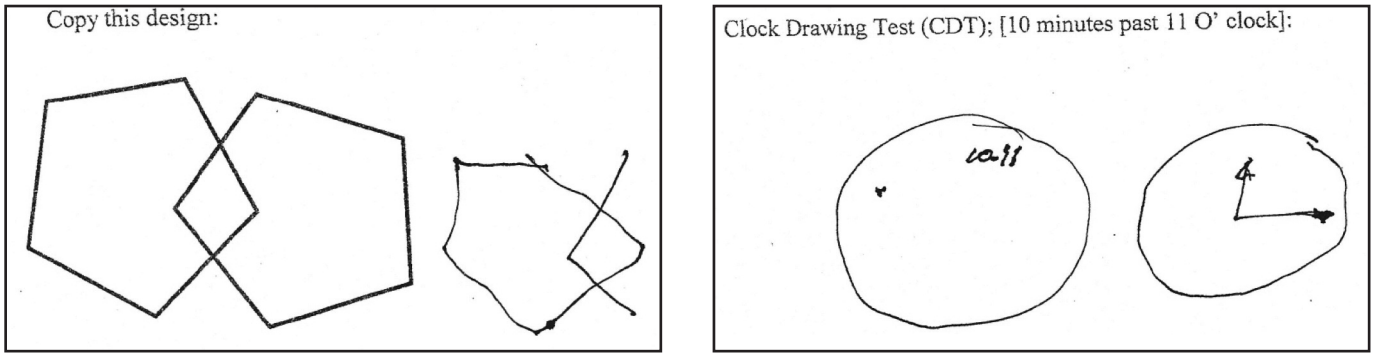

Fig. 1: copy pentagons and CDT on assessment when seen at the memory clinic.

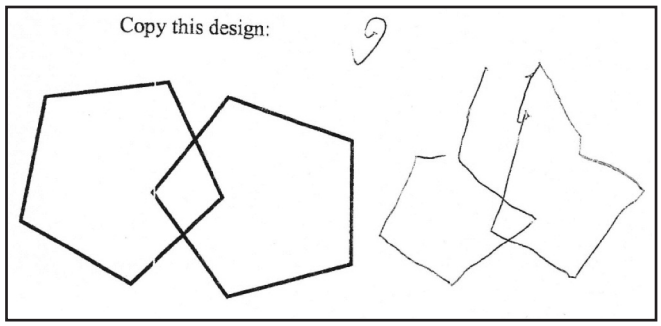

Fig. 2: copy pentagons done approximately 2 years ago.

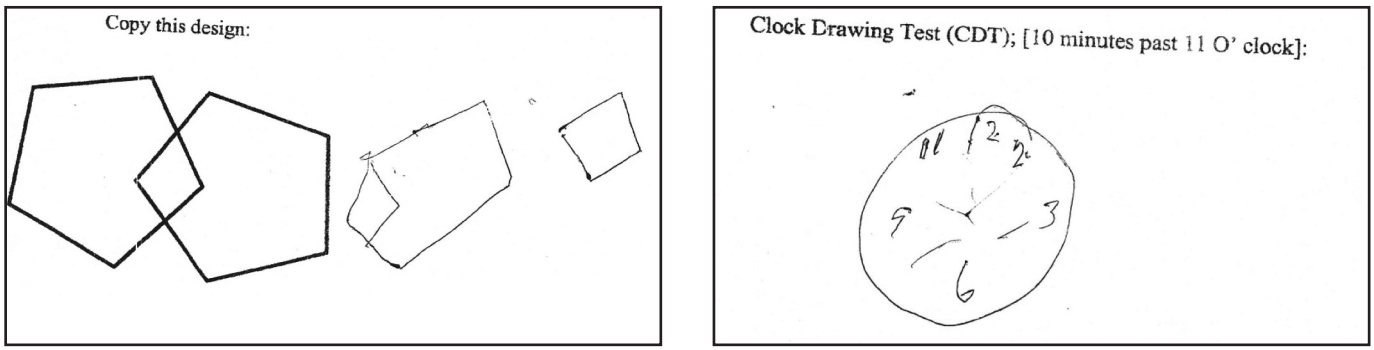

Fig. 3: copy pentagons and clock drawing test approximately a month after Risperidone was discontinued. MMSE was 24/30 with attention 2/5, orientation 8/10.

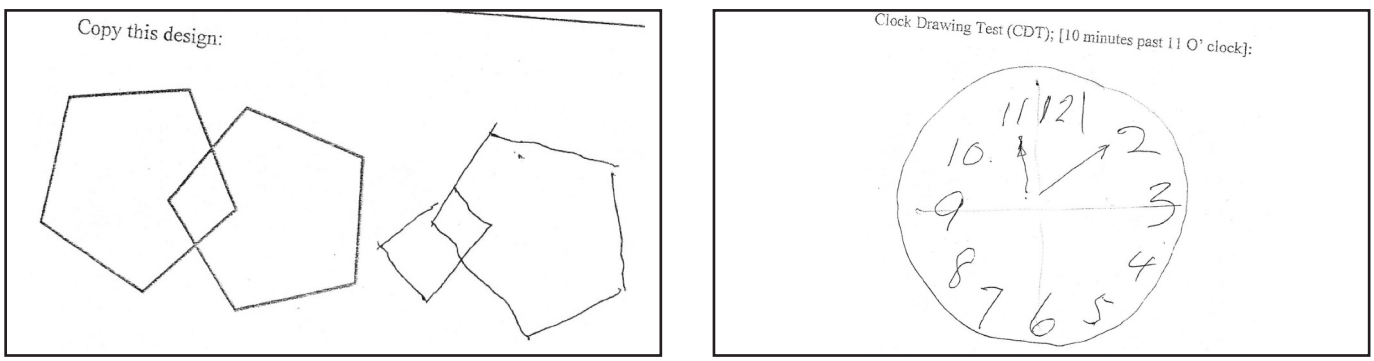

Fig. 4: copy pentagons and CDT 2 months after stopping Risperidone. MMSE was 25/30 with attention 4/5. Recall was 1/3.

causes, well- formed recurrent visual hallucinations and REM sleep behaviour disorder which may precede cognitive decline. Supportive clinical features include severe neuroleptic sensitivity, repeated falls, syncope, autonomic dysfunction, hallucinations in other modalities, delusions, apathy, anxiety and depression. Indicative biomarkers include low dopamine transporter uptake in the basal ganglia demonstrated by PET or SPECT imaging, abnormal 123Iodine- MIBG scintigraphy and polysomnographic confirmation of REM sleep without atonia.

No specific neurocognitive batteries for DLB have been developed but should include assessments for the full range of cognitive domains affected if possible. In general, bedside tests of cognitive function such as the MMSE do not reliably differentiate between dementia subtypes. However, the early appearance of impaired figure copying, clock drawing and attention is suggestive of DLB. When memory becomes affected, impaired memory retrieval may be more affected than acquisition. Radiological investigations usually show relative preservation of the medial temporal lobe on CT or MRI. There is generalised reduced uptake in the occipital lobe on PET or SPECT scanning. EEG may show prominent posterior slow wave activity and temporal lobe transient sharp waves.

A diagnosis of Probable DLB can be made when two or more core features are present with or without indicative biomarkers, or If only one core feature is present with one or more indicative biomarkers. A diagnosis of possible DLB can be made if only one core feature is present without any indicative biomarkers or one or more indicative biomarkers are present without any core features. In the absence of any core features, one or more suggestive features can be sufficient for a diagnosis for possible DLB. Probable DLB cannot be diagnosed based on suggestive features alone. DLB should be diagnosed when dementia occurs before or concurrently with Parkinsonism if it is present. In clinical research a 1-year difference between the onset of dementia and Parkinsonian features is required. The term Parkinson's Disease Dementia should be used in dementia that occurs in the context of well- established Parkinson's disease.

The patient above fulfils the criteria for Probable DLB with more than 2 core features. Correct diagnosis is often difficult in DLB because of the complexity of its presenting symptoms but is particularly crucial as misdiagnosis often leads to iatrogenesis as patients are often started on Neuroleptics. Neuroleptic sensitivity may occur in up to half of all cases and may precipitate or worsen confusion significantly. This usually occurs within 2 weeks of starting or a change in dose of neuroleptics and is associated with both typical or atypical neuroleptics. Neuroleptic use also increases the risk of mortality significantly.

As such the next course of action should initially be D) stopping his neuroleptic medications. Fig 3 and 4 show improvements in copy pentagons and click drawing test after stopping risperidone.

Other non-pharmacological as well as pharmacological interventions were then initiated.

"You treat a disease, you win, you lose. You treat a person, I guarantee you, you'll win, no matter what the outcome."
Robin Williams in Patch Adams.

MCQs (True/ False)

1. Regarding Dementia with Lewy Bodies (DLB):
A. It is the most common type of neurodegenerative dementia.
B. It is more common than Frontotemporal dementia.
C. There is often a strong family history.
D. Prevalence increases with age.
E. It is synonymous with Parkinson's Disease Dementia.

2. The following are core features of DLB:
A. Dementia.
B. Aural Hallucinations.
C. Fluctuations in attention.
D. Rigidity.
E. Autonomic dysfunction.

3. The following medications should be avoided in DLB if possible:
A. Haloperidol.
B. Rivastigmine.
C. Memantine.
D. Risperidone.
E. Donezepil.

4. Indicative biomarkers FOR DLB include
A. loss of Hippocampal volume on MRI.
B. Dopamine transporter uptake in the basal ganglia demonstrated by PET imaging.
C. abnormal 123Iodine- MIBG scintigraphy.
D. prominent posterior slow wave activity on EEG.
E. polysomnographic confirmation of REM sleep without atonia.

5. The following treatments have shown to be of benefit in DLB:
A. Acetylcholinesterase inhibitors.
B. High dose Vitamin E.
C. Physiotherapy.
D. Levodopa.
E. Fludrocortisone.

RECOMMENDED READING

1. McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor J-P, Weintraub D, et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium [Internet]. Neurology. Lippincott Williams & Wilkins; 2017 [cited 2019Jun11]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5496518/
2. Jellinger KA. Dementia with Lewy bodies and Parkinson's disease-dementia: current concepts and controversies [Internet]. SpringerLink. Springer Vienna; 2017 [cited 2019Jun11]. Available from: https://link.springer.com/article/10.1007/s00702-017-1821-9