Granulin-FTLD Presenting as Mixed Transcortical Aphasia: New Kid on the Block?

Dear Editor,

Mixed transcortical aphasia (MTA) results from extensive lesions involving the left cerebral hemisphere, which spares the perisylvian speech area.[1] It manifests as non-fluent speech with impaired naming and comprehension but preserved repetition.[2] MTA has been reported to most commonly occur in watershed infarctions involving the left anterior, middle, and posterior cerebral arteries.[3] The occurrence of hypoxia, carbon monoxide poisoning, and hypotension following hypoperfusion has also been described.[4]

MTA is usually seen as a sequela of a left-hemisphere watershed infarction that isolates Wernicke's perisylvian arc. Neurodegenerative diseases presenting as MTA have been described by Saadatpour *et al*.[3] and Whitaker and Whitaker.[5] The patient described by Saadatpour *et al*.[3] was a 55-year-old woman who began having word-finding difficulties and then gradually developed impaired spontaneous speech, comprehension, and naming, but with intact repetition. Magnetic resonance imaging (MRI) revealed atrophy in the left frontal, parietal, and temporal lobes. The patient described by Whitaker *et al*.[5] had severe echolalia, similar to our case. Automatic echolalia is a typical accompanying feature of transcortical aphasia, where repetition is preserved.[6] It occurs after lesions in the left hemisphere are located outside the perisylvian language area (PLA), which is responsible for verbal repetition. The PLA is anatomically intact but out of control by virtue of being disconnected from the eloquent cortical regions underlying language production and comprehension.

Perhaps this is the first report of a genetically mediated form of neurodegenerative dementia (granulin (GRN)-FTLD) presenting as MTA syndrome. PPA is a sporadic disease, but in a few cases, PPA has been reported in families with disease-causing mutations in *MAPT, GRN, C9orf72,* or *PSEN1*.[7] Of these, GRN is the most prevalent.[7] In a study of 502 probands (frontal variant FTD, FTD with motor neuron disease, primary progressive aphasia, and corticobasal syndrome), the clinical, neuropsychological, and brain perfusion characteristics of carriers of GRN mutations were described. Around 37% of carriers had a clinical diagnosis of PPA.[8] Aphasia was mostly non-fluent, consistent with PPA with agrammatism. Conduction and fluent aphasia were also observed in some cases. The authors did not report any cases of mixed transcortical aphasia. Van Deerlin *et al*.[9] reported 28 patients with FTLD with ubiquitin-positive and tau-negative inclusions. Nine patients had GRN mutations, of which two had a primary progressive aphasia phenotype (one non-fluent type, one mixed type). The report did not mention the status of repetition in patients with mixed aphasia. GRN mutations are known to present with degeneration in a more lateralized anatomic pattern (to the right or left), and the degeneration often spreads beyond the core behavioral variant FTD (bvFTD) regions, including the posterior cingulate, precuneus, and lateral parietal neocortex.[10] Consistent with this, our patient had atrophy and gliosis predominantly in the left frontotemporal region, with posterior involvement (parietal cortex). Identical GRN mutations can lead to bvFTD in some individuals and PPA in other members of the same family.[7] The current patient developed a behavioral syndrome 1 year after the illness, but his family history was negative for any dementia, language

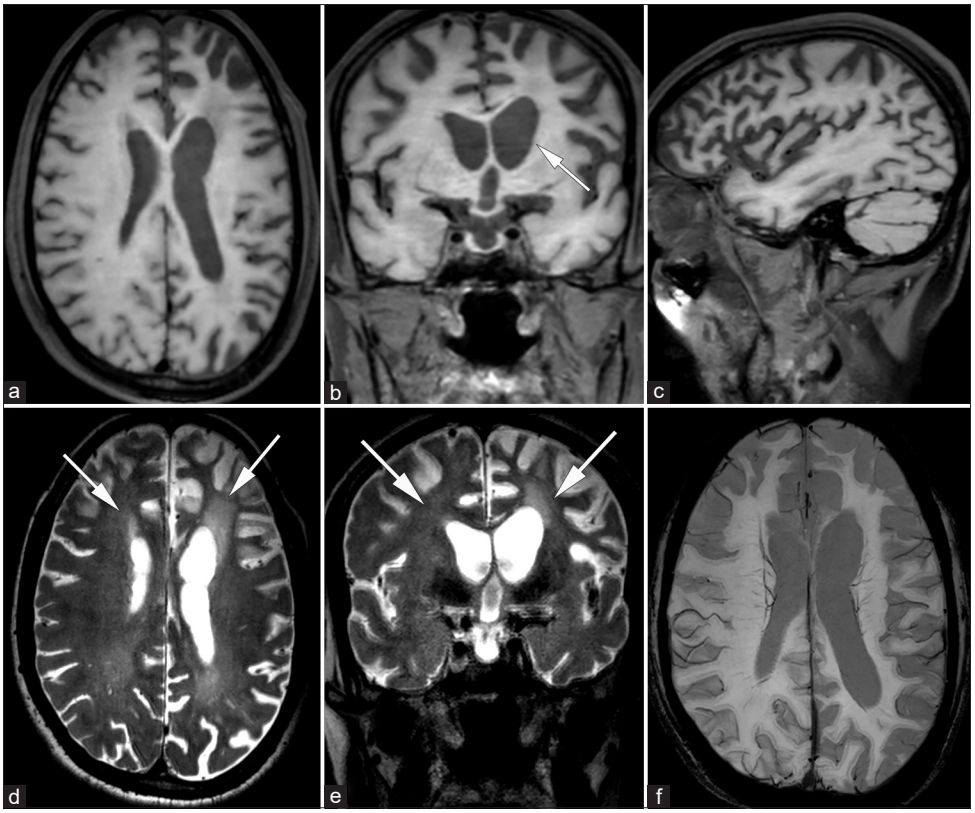

Figure 1: Axial (a), coronal (b), and sagittal (c) T1-weighted images show asymmetrical cortical atrophy in bilateral frontal lobes, parietal lobes (L > R), and the left caudate head (arrow in b). The frontal atrophy is more on the left side with an anterior-to-posterior gradient (c). The bodies of the left lateral ventricle and left frontal horn are dilated. Axial (d) and coronal (e) T2-weighted images show hyperintensity in both frontal white matter (L >> R) (arrows in d and e). Axial susceptibility-weighted image (f) shows no evidence of iron deposition or hemorrhage

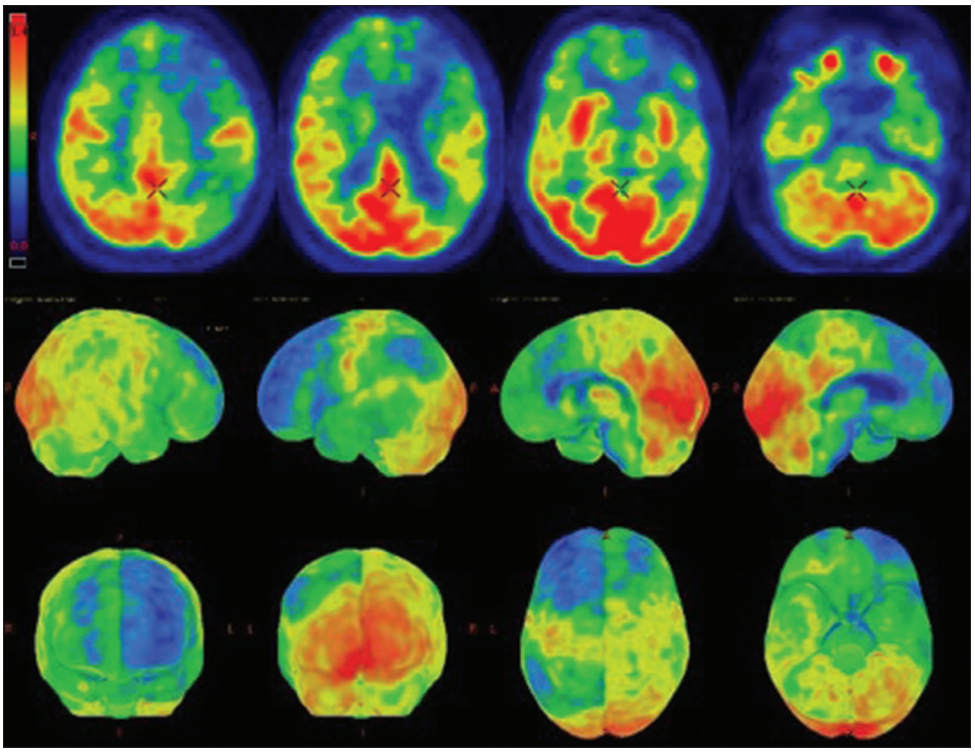

Figure 2: Transaxial F^{18}FDG Brain PET images (top row) showing hypometabolism in the frontal (L>R), left parietal, and left temporal cortices and the left caudate. Relatively preserved tracer uptake is noted in both sensorimotor, posterior cingulate, and occipital regions, including the visual cortices, remaining subcortical gray matter, and both cerebellar hemispheres. Cortex id rendering (bottom two rows) reiterates the same with hypometabolism in the frontal (L>R), left parietal, and left temporal cortices

disorder, or neurobehavioral symptoms. GRN mutations are universally accompanied by FTLD-TDP (frontotemporal lobar degeneration with transactive response DNA-binding protein 43 immunoreactive inclusion) pathology, type A.[10] We did not find a pathological correlation with this effect.

We present a patient with rapidly evolving mixed transcortical aphasia who was found to harbor a pathogenic genetic mutation for frontotemporal lobal degeneration. A 56-year-old man, a graduate, right-handed, working on a clerical post in a bank, presented with insidious onset and gradually worsening language function for 18 months. His son initially noticed that he had difficulty understanding what he used to read and started making spelling errors while writing. Over the next 2–3 months, he developed paraphasia, naming difficulties, and reduced fluency. Six months into the illness, he would speak only one or two words spontaneously but would repeat the comments/commands directed to him. A year into the illness, he became increasingly inattentive and distractible, would forget immediately what task had been given to him, and had difficulty calculating during money exchanges. His behavior changed progressively with the onset of stereotypies (repeatedly cleaning dirt, washing hands), changes in food preferences (eating raw potatoes), hyperorality (eating edibles that have fallen on the floor), and disinhibition. For the last two months before the presentation, he had intermittent episodes of bladder/bowel incontinence. There was no history of visual hallucinations, slowness in activities and gait, visuospatial dysfunction, seizures, past history of trauma, encephalitic illness, or stroke. His family history was insignificant.

A cognitive examination revealed severely impaired comprehension and fluency. The patient had no meaningful spontaneous speech. The patient was unable to follow simple commands. On asking his name/residence or giving pointing commands (pointing to the fan/light/door in this room), he would repeat the last two to three words of the command given by the examiner (automatic echolalia). He did not repeat comments or questions directed at other people (there was no ambient echolalia). In a repetition task, he could repeat the last two words of any given phrase. He could correctly identify two common objects, a pen and a watch, but had cognitive perseverance. On the picture-naming task from Addenbrooke's cognitive examination of three batteries, he could correctly name three objects (out of 12) on confrontation (goat, flag, and sickle). On category fluency, he named two animals (calf and a buffalo). In the picture description task, he correctly identified and named one object and persevered thereafter. He could not read single words or phrases and made vague, straight lines when asked to write sentences. His digit span forward recall was two, and the backward recall was zero. Further cognitive examinations could not be performed because of impaired comprehension and perseveration. A general neurological examination revealed utilization behavior, a pout reflex, mild rigidity in the limbs, and a mild stooped posture.

Routine blood investigations, including the thyroid profile and vitamin B12 levels, were normal. Cerebrospinal fluid examination results, including venereal disease research laboratory (VDRL), were within normal limits. MRI revealed asymmetrical bilateral cerebral atrophy, predominantly involving the bilateral frontal lobes (left more than right) and the left parietal region with associated gliosis [Figure 1]. The electroencephalogram did not reveal any focal discharges or slowing. ^{18}F-FDG-PET revealed hypometabolism in the frontal (L>R), left parietal and left temporal cortices, and left caudate [Figure 2]. Exome sequencing was performed in view of the young age, rapid progression of symptoms, and negative workup for rapidly progressive dementia. He was found to have a c.708 = 1G > A (5' splice site) heterozygous pathogenic mutation in the GRN gene on chromosome 7.

The patient was diagnosed as having genetic FTLD. He started with language dysfunction. On presentation, he had severely impaired comprehension, fluency, reading, and writing. The repetition and naming of common objects were partially preserved. His condition progressed rapidly, and within a year he developed other features suggestive of frontotemporal dementia (impaired verbal attention, perseveration, utilization, stereotypic behavior, hyperorality, disinhibition, and incontinence). Our analysis was limited by the lack of examination findings in the first year of the disease, but the pattern of language involvement at presentation (combination of comprehension and fluency impairment of nearly equal severity, with automatic echolalia indicating preserved repetition in the early phase of the disease) made us think of a 'mixed transcortical aphasia.' Mixed transcortical aphasia (MTA) is a rare language disorder characterized by impaired fluency and comprehension but relatively intact repetition.[2]

In conclusion, the phenotype of degenerative 'mixed transcortical aphasia' requires further clinical, genetic, and pathological correlations. Identifying such 'phenotype-genotype relationships is important, as targeted treatments may be possible in the future. This may be particularly important for GRN-FTLD, where progranulin protein levels are reduced because of haploinsufficiency, and efforts are underway to find strategies that can normalize circulating progranulin levels.

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Conflicts of interest

There are no conflicts of interest.

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