Quantitative Electroencephalography in Frontotemporal Dementia with Methylphenidate Response: A Case Study

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Key Words
Frontotemporal Dementia
LORETA
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SPECT

ABSTRACT
Frontotemporal dementia is an underdiagnosed illness with predominant behavioral and executive manifestations. Historically, diagnosis has been based on a combination of clinical history, neuropsychological testing, and brain imaging. No effective treatment currently exists for this disorder. A case is presented using quantitative EEG with methylphenidate challenge correlated with SPECT.

The patient underwent neuropsychological testing, a SPECT brain study, and a quantitative EEG, which was repeated after methylphenidate administration. SPECT was significant for hypoperfusion to the bilateral frontotemporal regions, with left-sided hypoperfusion greater than homologous right as demonstrated by LORETA analysis. QEEG correlated with SPECT, and demonstrated profound left greater than right bi-frontotemporal slowing, which normalized partially after methylphenidate administration. The patient has remained on methylphenidate as an outpatient, and has had significant behavioral improvement.

Quantitative EEG may provide both diagnostic and therapeutic data with regard to frontotemporal dementia. Further studies of methylphenidate in this population are needed to confirm these data.

INTRODUCTION
Case Study
A 72-year-old male with past medical history significant for hypertension, late onset diabetes mellitus, and an orthotopic liver transplant presented to the neuropsychiatric clinic for a personality change. The patient had experienced a progressive reduction in the ability to sustain attention, marked irritability, withdrawal, apathy, speech prompt mutism, and social disinhibition, characterized by repeated instances of theft and attempting to show pornography to family acquaintances, over an 8 month period. He also began to reuse alcohol sporadically after a well documented period of abstinence. The subject's neuropsychiatric history was significant for the presence of alcohol abuse last occurring over 12 years prior to his presentation, and a brief period of hepatic encephalopathy, which fully resolved prior to liver transplant. There was no significant family history of dementia or other neuropsychiatric disorder.

MRI-brain scan demonstrated only mild cortical atrophy and mild periventricular ischemic changes, but the severity of the findings did not correlate with the behavioral presentation of the patient. On neuropsychological testing the patient demonstrated intact intellectual functioning and memory, but profoundly impaired executive function and attention. Visuospatial and constructive ability were only mildly impaired, and reflected deficits in planning and organization consistent with frontotemporal dementia.

A SPECT-brain scan demonstrated a left greater than right bilateral reduction in perfusion to the frontotemporal areas, prompting a diagnosis of late onset frontotemporal dementia based on the criteria proposed by both the Lund and Manchester Groups as well as the Work Group on Frontotemporal Dementia and Pick's Disease. Quantitative electroencephalography (QEEG) acquisition correlated well with the SPECT images, and demonstrated partial resolution of the deficits after treatment with methylphenidate.

METHODS
The brain SPECT study was performed during an initial baseline period with the ligand injection given by a pre-established intravenous line prior to the administration of methylphenidate. A 25mCi (740-MBq) dose of technetium-99m-HMPAO (Amersham International) was infused...
without complication. The patient was unaware of the time of the actual injection, and QEEG recording was performed throughout the time of administration and ligand distribution. SPECT imaging data acquisition was performed approximately 90 minutes after ligand injection.

A rotating gamma camera system equipped with ultra high-resolution fan beam collimators (Trionic system) was used for SPECT data acquisition. Images were obtained in a 256 x 128 pixel format with an acquisition time of 50 seconds per step. Fan beam projection data were converted to parallel data in a 128 x 128 pixel format, and the SPECT reconstruction was performed with a Henning filter with 0.9 cycles/cm cutoff. Approximately 60 transverse slices were generated, and the images were processed using commercially available software (Medx) by Sensor systems. The SPECT study was spatially registered to allow for correlation with QEEG LORETA analysis.

For the QEEG portion of the exam, the subject was tested in a soundproof booth while awake and seated with his eyes closed. The EEG was recorded from 32 cephalic electrodes applied to the scalp in a pattern based on the International 10-20 System. The electrode impedance was < 5 Kohms, and impedance was monitored throughout the recording.

The tip of the nose was used as the reference, and the ear lobes had active leads for future linked-ears-reference computation. The acquisition-sampling rate was 500 Hz with filter settings at 0.015 Hz and 70 Hz. Actual QEEG recordings were performed at two distinct times, with one recording performed at baseline and another 1 hour after administration of methylphenidate 10mg as a single dose. The data analysis portion of the QEEG was accomplished with the NeuroGuide V1.5.

RESULTS
The SPECT imaging demonstrated a left greater than right bilateral reduction in perfusion to the frontotemporal areas consistent with frontotemporal dementia. No motor strip or parietal hypoperfusion abnormality was noted, and the examination was otherwise unremarkable, with the exception of the presence of mild atrophic changes, which correlated to the MRI results. (Figure 1).

The QEEG demonstrated at baseline significant excess of left temporal slow-wave activity in the 1-7 Hz range in addition to excessive occipital slowing at 4-7 Hz. The peak activity in the left temporal region was 1.5 Hz, which was topographically distributed as indicated by LORETA representation. On repeat study, 1 hour after the oral administration of methylphenidate 10mg, the temporal slowing in the delta frequencies was eliminated, although no significant change was noted in the 4-8 Hz (theta) frequency range. These LORETA based observations point to the area of hypoperfusion identified on the brain SPECT study conducted in parallel with the baseline QEEG. The most easily identified view of the hypoperfused area is seen in the coronal plane, and the corresponding arrows point to the location as defined by LORETA. (Figure 1).

DISCUSSION
Frontotemporal Lobar Degeneration (FTLD) is the third most common cause of dementia, and has been estimated to account for approximately 10% of dementia cases. It is characterized by a progressive deterioration of the frontotemporal lobes, and the disease has been noted to be asymmetrical in a subset of patients. FTLD can be subdivided into three differing clinical syndromes, the most common of which is frontotemporal dementia (FTD). The other syndromes include progressive nonfluent aphasia and semantic dementia.

FTD is manifest by profound alterations in personality and social conduct, and often is characterized by the presence of inertia and avolition. Alternatively, the patient can demonstrate social disinhibition and easy distractibility. Dysexecutive syndromes are common, but language and memory are relatively well preserved as compared to other deficits. The disorder presents classically in the sixth decade, but cases have been reported in the seventh and eighth decades as well. Two main histologic types which have been identified include a progressive microvascular change or alternatively severe astrocytic gliosis, which may or may not be accompanied by ballooned cells and inclusion bodies (Pick bodies).

The diagnosis of FTLD is primarily a clinical one, but can be supported by various imaging and neuropsychological testing techniques. Routine EEG is strikingly normal in patients with FTLD, as opposed to Alzheimer's disease (AD) patients who demonstrate a generalized progressive slowing of waveforms. Similarly, SPECT and PET scanning demonstrate differing patterns between the two diseases, with FTLD patients demonstrating hypoperfusion to the anterior frontal and temporal lobes, and AD patients classically demonstrating biperiatal hypoperfusion with motor strip sparing.

The role of QEEG is less defined in assisting a diagnosis of FTLD than is SPECT and PET, and to date, only two studies have addressed the issue. An initial study by Yener et al.

A more recent study from Stockholm, Sweden by Lindau et al.

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Figure 1
Neuromaging Techniques of Case Study. 1A—Topographic map of QEEG Z-scores at baseline and after methylphenidate administration; 1B—LORETA topographical distribution of peak activity at 1.5 Hz distributed to the left frontotemporal region; 1C—area of brain-SPECT hypoperfusion corresponding to the peak slowing at 1.5 Hz identified with LORETA.
to controls, the FTD patients demonstrated an absence of increased slow QEEG activity, and decreased fast activity whereas AD patients had a marked increase in slow activity and more marginally decreased fast activity. Model accuracy was an impressive 93%.

It is significant to note the differences identified in this study compared to prior QEEG findings in frontotemporal dementia. This patient presented with a classical frontotemporal degenerative syndrome that met restrictive criteria for FTD supported by neuropsychological testing and brain SPECT imaging. The discrepancy with prior published reports of FTD was identified only on QEEG analysis, which is not a standard tool used in the evaluation of FTD. This patient perhaps differed from previously reported cases in that he had clinically progressed over a 6 month time period, which raises the possibility of either focal findings in early FTD or the presence of a separate distinct QEEG pattern associated with clinical FTD that is responsive to psychostimulants.

Treatment of frontotemporal dementia is nonspecific to the illness, and often addresses only target problematic behaviors through a range of pharmacological interventions including alpha-2 agonists, mood stabilizers, and antipsychotic agents. The use of methylphenidate to target symptoms of executive dysfunction, attention, withdrawal and apathy is widely used in vascular dementia, and has been previously reported to be effective in Alzheimer’s dementia. No case of methylphenidate use in frontotemporal dementia correlated with QEEG imaging has been reported in the literature to date.

This patient was treated clinically with immediate release methylphenidate 10mg twice daily after completion of testing, but continued to have problematic behavior and apathy in the late afternoon and evening, so that patient was switched to a sustained release methylphenidate preparation 18mg daily with immediate and robust clinical results. In addition, to augment the effects of the methylphenidate, the patient was begun on bupropion sustained release 100mg daily. The patient’s personality reverted to a near premorbid state, and the patient demonstrated virtually no signs of withdrawal, apathy, or irritability. His mood and affect improved, and the patient’s impulsivity dramatically decreased without further episodes of alcohol consumption or shoplifting for several months. To date, the patient has largely sustained the observed clinical improvements over an 11 month period, with the exception of impulsivity in the form of recurrent petty shoplifting, which reemerged as a behavior approximately 4 months after treatment was initiated. However, in contrast to prior behavior, the impulsivity remains manageable with verbal redirection by caregivers.

The striking improvement noted in this case is postulated to be related to an improvement in cortical activity in the frontotemporal areas of the left cortex as demonstrated on QEEG. By stimulating the areas demonstrating an excess of theta and delta activity with a neurostimulant, it appears that the areas of abnormally slowed cortical activity are partially corrected leading to improved executive function and partial clinical recovery. These results may suggest a role for methylphenidate in the treatment of early frontotemporal dementia. In addition, partial normalization of cortical activity on the QEEG with methylphenidate use may be correlative with sustained clinical improved, as was observed in this patient. Further studies are needed to support these points.

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REFERENCES