Uncertainties Hinder IEED Treatment Options

Depression often accompanies involuntary emotional expression disorder; SSRIs can sometimes treat both.

BY KERRI WACHTER
Senior Writer

BALTIMORE — The lack of diagnostic criteria has hamstrung neurologists in their attempt to diagnose involuntary emotional expression disorder, Dr. Sharon Handel said at a meeting on Alzheimer's disease and related disorders sponsored by Johns Hopkins University.

Even when they make the diagnosis with certainty, neurologists have little to offer by way of Food and Drug Administration–approved therapy, said Dr. Handel, of the department of psychiatry at Johns Hopkins University, Baltimore.

Part of the problem with identifying this condition has been the numerous names under which it is known, she noted. Involuntary emotional expression disorder (IEED) is also known as pseudobulbar affect and pathologic laughing or crying.

It's been estimated that more than 1 million people in the United States have IEED. The disorder has been associated with cerebrovascular accident, Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis, and traumatic brain injury.

The hallmark of IEED is episodes of crying or laughing that are unrelated to or out of proportion with the eliciting stimulus. There is a disconnection between emotional experience and expression.

Emotional outbursts in IEED are involuntary, episodic, and incongruent with baseline mood. The outbursts are intense, but are followed by a return to baseline.

Disorders of affect—which IEED appears to be—involve impairment of the moment-to-moment regulation of emotion. "There's a disconnection of the neural networks in this condition from the experienced emotion to the display of emotion," said Dr. Handel.

The neural networks of emotion involve the frontal lobes, the limbic system, the brainstem, the cerebellum, and white-matter tracts. In particular, the prefrontal cortex integrates complex sensory and limbic information that determines the emotional valence of a stimulus and modulates motor and autonomic responses involved in emotional expression. It's not clear where the neural interruption occurs in IEED.

For now, the current diagnostic criteria include:

- Episodes of involuntary crying, laughing, or related displays.
- An origin in brain injury or disease.
- A change in the patient's emotional behavior from that prior to the disease or injury.
- Incongruent or exaggerated mood.
- A response that is excessive or unrelated to the stimulus.
- Significant distress or impairment.

The differential diagnosis should include epilepsy; facial dystonia or dyskinesias; vocal tics; axis I disorders (such as major depression or bipolar disorder); axis II disorders (such as borderline personality disorder); and substance abuse.

"These patients often have major depression, and while specific treatment is often the same, I think it's important to differentiate the two conditions," said Dr. Handel.

The differential diagnosis should also include affective lability, essential crying, and witzelsucht (a tendency to inappropriate jokes). With affective lability, the subjective and objective dimensions of affect are not dissociated. Essential crying is a hereditary and lifelong tendency to cry easily. Witzelsucht is an addiction to trivial joking, which can take the form of both an inappropriate giddy affect and irritability or aggressiveness.

In terms of clinical course, IEED frequently remits spontaneously within 6 months. Others may have remission with treatment within 3 months. Resolution of IEED can be independent of the resolution of depression. However, in some cases the disorder is chronic and persistent without treatment.

Treatment of IEED is still evolving. At present, there is no FDA-approved treatment for IEED. "What are typically used—at least up to this point—are SSRIs. They tend to work quite quickly," said Dr. Handel.

In fact, response can be seen in just a few days in some patients.

Dextromethorphan, in combination with quinidine, is being studied to treat patients with IEED. Dextromethorphan is a nonopioid antitussive, but it also has a number of other neuropharmacologic properties. It is a potent sigma$_1$ agonist (inhibiting the release of the excitatory neurotransmitter, glutamate) and is also an *N*-methyl-D-aspartic acid glutamate receptor antagonist.

Dextromethorphan undergoes significant first-pass metabolism by the cytochrome P450 isoenzyme CYP2D6. Quinidine is a potent inhibitor of this isoenzyme, thereby increasing and sustaining dextromethorphan levels. ■

Booklet Explains Alzheimer's Disease

The National Institute on Aging is offering a free booklet that is designed to help people who have limited reading skills learn about Alzheimer's disease. "Understanding Alzheimer's Disease" includes information about the signs of the disease, treatment options, and also offers help for caregivers. Visit www.nia.nih.gov/alzheimers/publications/understandingad to download this booklet or order by calling 800-438-4380.

Gene Mutations Linked to 5% Of Frontotemporal Dementia

BY JAMES BUTCHER
Contributing Writer

SALZBURG, AUSTRIA — Mutations in the progranulin gene are found in approximately 5% of patients with frontotemporal dementia, according to research presented at the 8th International Conference on Alzheimer's and Parkinson's Diseases.

Frontotemporal dementia (FTD) is the second most common cause of dementia, after Alzheimer's disease, in patients aged 65 years or less.

Approximately 35%-50% of those patients with frontotemporal dementia have a family history of dementia, a statistic which suggests that there is a strong genetic component to the disease.

Of 272 patients with FTD, 14 were found to have progranulin mutations, for a frequency of 5%. 'All the cases had a family history of disease.'

In 1998, investigators reported that they found mutations in the gene encoding the microtubule-associated protein tau (MAPT) caused familial FTD with parkinsonism linked to chromosome 17 (FTDP-17).

However, not all families who showed linkage to the same region on chromosome 17 had mutations in MAPT, suggesting that mutations in at least one other gene were responsible for the disease in these patients.

In addition, these patients had ubiquitin-immunoreactive neuronal cytoplasmic inclusions (FTDU-17) but not tau-immunoreactive inclusion pathology.

In July 2006, two studies found that FTDU-17 is caused by mutations in progranulin, a polypeptide with growth-modulatory activity, leading to a loss of protein function (Nature 2006;442:916-9; Nature 2006;442:920-4).

Since then, researchers have been screening their patient populations for the mutations to determine their prevalence in the frontotemporal dementia community.

Stuart Pickering-Brown, Ph.D., who works at the University of Manchester (England), presented data from the Manchester Cohort that currently includes 272 patients with FTD; some of the included patients have been followed for more than 20 years.

"We recently finished sequencing for progranulin mutations and found 14 cases," commented Dr. Pickering-Brown.

He also noted that this frequency (5%) is about the same as for tau gene mutations (6%) in his study cohort.

Clinically, the 14 patients with the progranulin mutations had been diagnosed with frontotemporal dementias, primary progressive aphasia, and corticobasal degeneration, according to Dr. Pickering-Brown.

He added that "All the cases had a family history of disease."

The researchers also genotyped a number of single nucleotide polymorphisms (SNPs) spanning the progranulin gene to determine whether a common variation at the locus increases the risk of sporadic disease, but they reported finding no evidence of allelic association of any of the SNPs.

Dr. Brendan Kelley presented the latest data from the Mayo Clinic cohort of patients at the meeting.

He reported on the clinical characterization of eight kindreds, which included 31 individuals with progranulin mutations, of whom 16 were men.

The patients were aged 49-83 years at disease onset (mean age 63 years) and had a disease duration of 1-12 years (mean 6.5 years).

"Two individuals who died within 1 year both had accidents that may have been related to disinhibited behaviors," said Dr. Kelley.

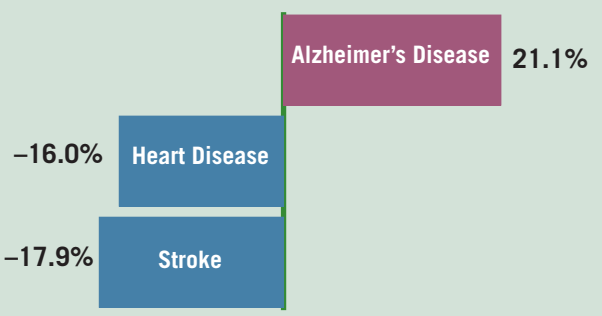
Like the Manchester cohort, the clinical diagnosis varied widely and included frontotemporal dementia with and without parkinsonism, mild cognitive impairment, Alzheimer's disease, corticobasal syndrome, and primary progressive aphasia.

"At this juncture, clinical practice will not be changed based on the discovery of this gene," commented Dr. Zbigniew Wszolek, who is currently a professor of neurology at the Mayo Clinic College of Medicine, Jacksonville, Fla., and who chaired the session at the meeting.

"Clinical genetic testing, I believe, is not available yet, albeit patents have been filed," noted Dr. Wszolek. ■

DATA WATCH

Alzheimer's Mortality Increasing; Deaths From Stroke and Heart Disease Decreasing



Note: Percentage change in mortality per 100,000 population.
Source: Centers for Disease Control and Prevention

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