Expanding the Differential Diagnosis of Chronic Dizziness

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**Objective:** To improve treatment outcomes for patients with chronic dizziness by identifying clinical conditions associated with persistent symptoms and delineating key diagnostic features that differentiate its causes and direct attention to specific treatments.

**Design:** Prospective cohort study from 1998 to 2004.

**Setting:** Tertiary care balance center.

**Patients:** A total of 345 men and women, aged 15 to 89 years, referred for evaluation of chronic dizziness (duration of ≥3 months) of uncertain cause.

**Interventions:** Patients were systematically directed through multiple specialty examinations until definitive diagnoses were made.

**Main Outcome Measure:** Final diagnoses associated with dizziness.

**Results:** Nearly all patients with chronic subjective dizziness were diagnosed with psychiatric or neurologic illnesses. These included primary and secondary anxiety disorders (n=206 [59.7%]) and central nervous system conditions (n=133 [38.6%]), specifically migraine headaches, mild traumatic brain injuries, and neurally mediated dysautonomias. A small number of patients (6 [1.7%]) had dysrhythmias. Four of 5 patients with migraine or dysrhythmias had comorbid anxiety.

**Conclusions:** Chronic dizziness has several common causes, including anxiety disorders, migraine, traumatic brain injuries, and dysautonomia, that require different treatments. Key features of the clinical history distinguish these illnesses from one another and from active neurotologic conditions. The high prevalence of secondary anxiety may give a false impression of psychogenicity.

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active vestibular deficits. Earlier investigations suggested that CSD could be triggered by medical or psychiatric processes and found that it was one entity in a group of clinical conditions that constituted the differential diagnosis of chronic nonvertiginous dizziness.²⁻⁹ However, the relationships among CSD, anxiety disorders, neurotologic conditions, and other medical causes of chronic dizziness are not fully understood. The current investigation sought to clarify the prevalence and comorbidity of medical and psychiatric causes of chronic dizziness. A total of 345 patients who were referred for evaluation of persistent nonvertiginous dizziness were followed prospectively through multiple specialty evaluations until the primary illnesses associated with their symptoms were identified. Then, the key features of clinical history that differentiated these illnesses were delineated. These results may improve diagnostic precision and therapeutic outcomes for patients with this frequently enigmatic clinical presentation.

**METHODS**

**PATIENT POPULATION**

Data for this report were abstracted from a research database containing deidentified information on all patients older than 12 years who underwent neurotologic and psychiatric evaluations for chronic dizziness at our university-based, tertiary care balance center from 1998 to 2004. The database includes patient demographics, presenting symptoms, duration of illness, medical and psychiatric diagnoses, and treatment histories prior to referral. Results of diagnostic evaluations and outcomes of treatment performed in our balance center were entered into the database prospectively. The institutional review board at the University of Pennsylvania School of Medicine, Philadelphia, approved the conduct of this study.

From July 1998 through September 2004, approximately 2400 patients were referred to our balance center for evaluation of dizziness. Balance center examinations revealed no active medical causes of dizziness in 25% of these individuals, who presented with nonvertiginous dizziness or subjective imbalance lasting 3 months or more. We followed 345 of these patients prospectively through additional specialty consultations until the causes of their dizziness were discovered. The remaining patients could not be seen for all of their studies because of insurance restrictions or logistical difficulties (eg, travel distance) and were excluded from this study.

**CLINICAL EVALUATION AND DIAGNOSTIC CRITERIA**

Since 1998, our balance center has employed a protocol-driven, multidisciplinary evaluation process to ensure that all patients receive needed specialty examinations and laboratory testing. Patients in this study received the following balance center assessments:

- **Neurotologic evaluation:** Neurotologic histories and examinations were conducted by a board-certified neurotologist (M.J.R.). Laboratory evaluation included audiometric assessments, balance function tests (oculomotor examination, Dix-Hallpike and caloric tests, rotary chair, computerized dynamic posturography, sensory organization test, and vestibular evoked myogenic potentials, as indicated). All patients underwent magnetic resonance imaging of the brain with gadolinium at our center or prior to referral.

- **Psychiatric assessment:** Psychiatric examinations were conducted by a board-certified psychiatrist who is experienced in neurology and vestibular physiology (J.P.S.). This evaluation was adapted from the patient version of the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (SCID-IV/P), the standard diagnostic instrument for psychiatric clinical research.

- **Systematic screening for other causes of dizziness:** Patients were screened for other medical causes of dizziness with a checklist that included queries about recurrent headaches, head trauma, whiplash injury, seizures, peripheral neuropathy, visual disturbance, dysequilibrium, and autonomic dysfunction. Those who screened positive for these conditions were referred for additional consultations within the balance center or to outside specialists (eg, neurologists, cardiologists, rheumatologists, neuro-opthalmologists, and psychiatrists).

Final diagnoses for study patients were rendered according to the criteria in this section.

**FEATURES OF CSD**

Chronic subjective dizziness is a specific clinical syndrome with the cardinal feature of persistent nonspecific dizziness that cannot be explained by active medical conditions. It is not a diagnosis of exclusion. It was identified by the following physical symptoms and examination findings:

- **Persistent** (duration of ≥3 months) sensations of nonvertiginous dizziness, lightheadedness, heavy-headedness, or subjective imbalance present on most days.

- **Chronic** (duration of ≥3 months) hypersensitivity to one’s own motion, which is not direction specific, and to the movements of objects in the environment.

- **Exacerbation** of symptoms in settings with complex visual stimuli such as grocery stores or shopping malls or when performing precision visual tasks such as reading or using a computer.

- **Absence** of currently active physical neurotologic illnesses, definite medical conditions, use of medications that may cause dizziness, or inability of such conditions to account for the full extent of dizziness or disability. Medical history could include episodes of true vertigo or ataxia as long as the conditions causing those symptoms were resolved.

- **Results** from radiographic imaging of the brain that exclude neurotologically significant anatomical lesions.

- **Findings** from balance function tests that are in the reference range or are nondiagnostic. Included in this criterion were patients who had recovered clinically from past neurotologic illnesses and demonstrated fully compensated vestibular deficits on balance function tests and those with isolated test abnormalities that could not explain their presenting symptoms.

To be included in this study, patients had to meet all of the diagnostic criteria for CSD. Based on previous studies, it was expected that about two thirds of patients would have medical histories of transient neurotologic conditions such as vestibular neuronitis or benign paroxysmal positional vertigo that had resolved, leaving nonspecific dizziness in place of previous vestibular vertigo. Furthermore, it was expected that a smaller number of patients would have medical histories suggesting potentially recurrent neurotologic conditions, such as Ménière’s disease or autoimmune ear disease. These patients were included only if their clinical presentations met the CSD criteria described above (ie, ≥3 months of nonvertiginous dizziness) and they had no audiometric abnormalities or uncompensated vestibular deficits.
ANXIETY DISORDERS

On the basis of previous studies, anxiety disorders from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) were regrouped into 3 categories that are relevant for patients with chronic dizziness.1-3

• Panic and phobic disorders: This category included panic disorder with or without agoraphobia, agoraphobia without panic, social phobia, and specific phobia of dizziness. Specific phobias unrelated to dizziness were excluded. Panic and phobic disorders share several core symptoms in patients with dizziness, including trepidation in advance of situations associated with dizziness (anticipatory anxiety), avoidance of such situations because of fears about the consequences of being dizzy (phobic avoidance), and the propensity for panic symptoms to accompany dizziness.

• Generalized anxiety: This category included generalized anxiety disorder, a condition identified by excessive worry about routine life events. Patients with this disorder are often described as worrywarts by individuals who know them well.

• Minor anxiety: This category included patients with low levels of anxiety about dizziness that caused, at most, minor interference with daily functioning. Also included were patients who experienced persistent dizziness without overt anxiety. Their clinical histories were otherwise identical to patients who acknowledged anxiety. This type of monosymptomatic somatoform presentation is increasingly considered to be a forme fruste of anxiety.

CSD WITH ANXIETY

Patients who met criteria for CSD and anxiety were given a final diagnosis based on previous work that identified 3 patterns of illness.1-3

• Otogenic CSD: Patients with otogenic CSD had no history of anxiety predating dizziness. They developed CSD and anxiety following temporary medical conditions that affected their balance systems (e.g., vestibular neuritis, transient ischemic attack, or deconditioning of balance reflexes after prolonged illness).

• Psychogenic CSD: Patients with psychogenic CSD had no medical causes of dizziness. They developed dizziness during the course of their anxiety disorders.

• Interactive CSD: Patients with interactive CSD had strong anxiety diatheses or anxiety disorders that predated dizziness. They developed CSD and worsening anxiety following a transient medical condition that caused dizziness.

OTHER PSYCHIATRIC DISORDERS

In previous investigations, a small portion of patients with chronic dizziness met DSM-IV criteria for major depression, hypochondriasis, or conversion disorder.1-4 Patients with hypochondriasis have overvalued beliefs that they suffer from specific, usually serious medical illnesses, despite evidence to the contrary. Patients with conversion disorder have sensory or motor dysfunction in the absence of a medical cause. The SCID-I/P10 includes diagnostic queries for these disorders.

MIGRAINE

Patients who screened positive for recurrent headaches were examined for the presence of migraine headache with or without aura or probable migraine in strict accordance with the 1988 criteria of the International Headache Society12. Patients diagnosed with migraine headache met all 4 of the following criteria of the International Headache Society: (1) recurrent headaches severe enough to interfere with routine daily activities; (2) unilateral or bitemporal headache location or pulsatile headache quality; (3) headaches accompanied by nausea/vomiting, photophobia, or phonophobia; and (4) headaches lasting 4 to 72 hours.

Vestibular migraine (migrainous vertigo) is a clinical entity that is increasingly recognized in the neurotologic literature13 but is not included in the 1998 criteria of the International Headache Society.14 Definitions of vestibular migraine vary. Narrow definitions of vestibular migraine include only dizziness that occurs in conjunction with headaches. However, the broader definitions of this condition include vertiginous and nonvertiginous dizziness in persons with recurrent headaches, whether or not the dizziness is temporally related to headaches. The situation is complicated further by the fact that migraine and anxiety are highly comorbid. At least 30% of patients with migraine have coexisting anxiety disorders.15 Therefore, at the outset of this study, a decision was made to exclude individuals who presented to the balance center with ongoing episodes of headache-related vertigo or ataxia but to include patients with a headache history who presented with nonvertiginous dizziness and met all other criteria for CSD. Thus, migraine was handled in the same manner as other potentially recurrent neurotologic conditions (e.g., Menière’s disease), keeping the focus on persistent nonspecific dizziness and excluding those with ongoing true vertigo. Another decision was made that migraine would take precedence over anxiety in assigning patients with chronic dizziness to a diagnostic group. Migraine is a recurrent illness, unlike transient neurotologic conditions that typically trigger CSD. Therefore, separate pathophysiologic processes might be responsible for chronic dizziness in migraine vs other causes of CSD. Clinical experience suggests that migraine may be masked by anxiety in patients with chronic dizziness, and patients may require antimigraine therapy to control their symptoms, even if comorbid anxiety is well controlled. Therefore, the classification scheme was designed to be sensitive to migraine.

POSTCONCUSSIONAL SYNDROME

Patients who screened positive for persistent nonspecific dizziness that began shortly after head trauma or whiplash injury were evaluated for the presence of postconcussional syndrome. In addition to chronic dizziness, criteria for postconcussional syndrome include16:

• Dysphoria, irritability, or mood lability

• Insomnia, fatigue, or poor stamina

• Headache

• Short-term memory loss or attention and concentration problems.

Individuals with a history of head trauma who presented to the balance center with vertigo or ataxia were excluded from the study. Patients who reported head trauma or whiplash without subsequent dizziness were included in the study but classified according to other causes of chronic dizziness. We gave TBI precedence over depression or anxiety in assigning patients to diagnostic groups. As is the case with migraine and anxiety, TBI may be masked by comorbid depressive or cognitive disorders and may require specific treatment interventions. Therefore, the classification scheme was designed to be sensitive to TBI.

OTHER MEDICAL CONDITIONS

Patients were queried about symptoms of dysrhythmias (paroxysmal lightheadedness, presyncope, and palpitations) and au-
The study cohort included 115 men (33.3%) and 230 women (66.7%) with a mean (SD) age of 43.5 (15.3) years (range, 15-89 years). Most (92.7%) were white. All but 6 patients were diagnosed as having psychiatric or neurologic conditions, including primary or secondary anxiety disorders, migraine, TBI, and neurally mediated dysautonomias. Six had cardiac dysrhythmias (Table 1). The percentage of women was somewhat smaller among patients with postconcussional syndrome than in the rest of the study cohort ($\chi^2 = 3.08; P < .08$) (Table 2). Otherwise, there were no significant age or sex differences across diagnostic groups. Table 3 lists the key features of the study cohort.

### Table 1. Medical and Psychiatric Diagnoses in 345 Patients With Chronic Subjective Dizziness (CSD)

<table>
<thead>
<tr>
<th>Conditions Associated With CSD</th>
<th>No. (%)</th>
<th>Neurologic and Other Medical Conditions</th>
<th>DSM-IV Psychiatric Disorders‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSD and anxiety</td>
<td>206 (59.7)</td>
<td>None (115)</td>
<td>Panic/phobic (65), Generalized anxiety (25), Minor anxiety (25)</td>
</tr>
<tr>
<td>Psychogenic</td>
<td>115 (33.3)</td>
<td>Peripheral deficits (21)† Central deficits (10)† Deconditioning (4)‡</td>
<td>Panic/phobic (14), Generalized anxiety (4), Minor anxiety (17)</td>
</tr>
<tr>
<td>Otogenic</td>
<td>35 (10.1)</td>
<td>Peripheral deficits (38)* Central deficits (6)†</td>
<td>Panic/phobic (20), Generalized anxiety (31), Minor anxiety (2)</td>
</tr>
<tr>
<td>Interactive</td>
<td>53 (15.4)</td>
<td>Adverse drug reactions (5)‡ Other medical (4)†</td>
<td>None (3), Hypochondriasis (1), Conversion (2)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (0.9)</td>
<td>None (3)</td>
<td>None (3)</td>
</tr>
<tr>
<td>CSD and CNS illness</td>
<td>133 (38.6)</td>
<td>Migraine (57)</td>
<td>Panic/phobic (21), Generalized anxiety (10), Minor anxiety (13), Major depression (3), None (10)</td>
</tr>
<tr>
<td>Migraine</td>
<td>57 (16.5)</td>
<td>Migraine (57)</td>
<td>None (10)</td>
</tr>
<tr>
<td>TBI</td>
<td>52 (15.1)</td>
<td>Mild TBI (50)</td>
<td>Panic/phobic (5), Posttraumatic stress (7), Postconcussional syndrome (40)</td>
</tr>
<tr>
<td>Dysautonomia</td>
<td>24 (7.0)</td>
<td>Neuromediated reflex syncope (24)‡</td>
<td>Panic/phobic (2), Generalized anxiety (4), Minor anxiety (3), None (15)</td>
</tr>
<tr>
<td>CSD and dysrhythmia</td>
<td>6 (1.7)</td>
<td>Atrial or ventricular dysrhythmias (6)</td>
<td>Panic/phobic (2), Generalized anxiety (3), Conversion (1)</td>
</tr>
<tr>
<td>Dysrhythmia</td>
<td>6 (1.7)</td>
<td>None (3)</td>
<td>None (3)</td>
</tr>
</tbody>
</table>

### Table 2. Demographics of Patients With Various Causes of Chronic Subjective Dizziness (CSD)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Age, Mean (SD), Range, y</th>
<th>Female Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSD and anxiety</td>
<td>45.8 (14.5), 19-72</td>
<td>65.5</td>
</tr>
<tr>
<td>Otogenic</td>
<td>43.3 (15.9), 15-89</td>
<td>67.7</td>
</tr>
<tr>
<td>Psychogenic</td>
<td>47.4 (13.8), 18-81</td>
<td>77.3</td>
</tr>
<tr>
<td>Interactive</td>
<td>42.3 (11.2), 19-72</td>
<td>77.1</td>
</tr>
<tr>
<td>CSD and migraine</td>
<td>45.1 (14.0), 16-71</td>
<td>56.8*</td>
</tr>
<tr>
<td>CSD and postconcussional syndrome</td>
<td>37.5 (16.6), 15-72</td>
<td>63.2</td>
</tr>
</tbody>
</table>

*P < .08.
The largest diagnostic category of illnesses associated with CSD, with nearly 60% of the patient population, was anxiety disorders. In this group, psychogenic CSD (n=115 [33.3%]) was twice as prevalent as interactive CSD (n=53 [15.4%]) and 3 times as prevalent as otogenic CSD (n=35 [10.1%]). Anxiety disorders varied across the 3 subtypes of CSD (\( \chi^2 = 35.95; P < .001 \)). Panic disorder predominated in patients with psychogenic CSD, whereas generalized anxiety was most common in patients with interactive CSD. Patients with otogenic CSD had the mildest anxiety symptoms. In otogenic and interactive CSD, the initial precipitant for dizziness was usually a transient neurologic condition, such as vestibular neuronitis or benign paroxysmal vertigo, which occurred an average of 4 years prior to balance center referral. Other medical triggers included adverse effects of prescription medications, physical deconditioning of balance reflexes after prolonged illness, and medical conditions not typically associated with dizziness (e.g., pre-eclampsia). A remarkably small number of patients had hypochondriasis or conversion disorder.

Illnesses of the central nervous system constituted the second largest category of diagnoses associated with CSD (n=133 [38.6%]) and included 3 conditions, migraine (n=57 [16.5%]), postconcussional syndrome (n=52 [15.1%]), and neurally mediated dysautonomias (n=24 [7%]). Because of the study's focus on chronic nonspecific dizziness, patients with migraine who presented to the balance center with ongoing episodes of vertigo or ataxia were excluded. Nevertheless, approximately one third of patients in the migraine group had experienced vertigo or ataxia during headaches in the past. The others had only nonspecific dizziness. Clinically significant anxiety was present in 77% (44 of 57) of study patients with migraine and often dominated the clinical picture.

Patients diagnosed as having postconcussional syndrome developed chronic dizziness shortly after blows to the head or whiplash injuries. Their primary complaints were chronic nonspecific dizziness and hyper-sensitivity to motion stimuli, but they also were impaired by poor stamina and short-term memory and concentration problems. They had notable levels of dysphoria and irritability, which were not diagnosed separately as depressive illnesses because they are part of the definition of postconcussional syndrome. A small minority had clinical histories consistent with labyrinthine trauma or posttraumatic benign paroxysmal vertigo in the early aftermath of their injuries, but these symptoms resolved prior to balance center referral. Patients with postconcussional syndrome had relatively low rates of anxiety disorders, including injury-related post-traumatic stress disorder.

Among individuals diagnosed with dysautonomias (n=24 [7%]), 2 types of neurally mediated reflex responses were observed on tilt table testing. The type 1 mixed response was marked by tachycardia on assuming the head upright position, followed within 10 to 20
minutes by symptomatic hypotension and a drop in heart rate without asystole. The postural orthostatic tachycardia syndrome manifested as persistent tachycardia on upright tilt without changes in blood pressure.\textsuperscript{15} Patients in this group did not have histories of syncope, probably because that would have prompted a cardiology, not neurotology, consultation. Most patients with dysautonomia did not have psychiatric comorbidity.

Six patients (1.7%) had dysrhythmias, the most significant of which were atrial fibrillation and Wolf-Parkinson-White syndrome. Interestingly, all 6 patients with dysrhythmias had psychiatric disorders.

**COMMENT**

The results of this study extend our previous study of the differential diagnosis of persistent nonvertiginous dizziness\textsuperscript{2,5} and complement the findings of other investigators who have examined similar symptoms in patients with anxiety disorders,\textsuperscript{16,17} migraine,\textsuperscript{13,18} TBI,\textsuperscript{6} and dysautonomia.\textsuperscript{15} Taken together, these studies demonstrate that CSD may be caused by multiple illnesses that include, but are not limited to, psychiatric disorders. Therefore, the classic concept of “psychogenic” dizziness must be recognized as a misnomer that may cause errors of omission in medical evaluations of patients with chronic dizziness.

Most patients (~60%) in this large investigation had CSD with anxiety, but only one third of the study cohort, those with psychogenic CSD, had primary psychiatric causes of dizziness. The others had transient medical causes of dizziness followed by anxiety (ie, otogenic or interactive CSD) or illnesses of the central nervous system manifesting as CSD. A small percentage of patients had cardiac dysrhythmias. This result is consistent with the first report of CSD.\textsuperscript{2} However, that investigation found equal numbers of patients with all 3 CSD subtypes because anxiety symptoms guided the assignment of patients to diagnostic categories. As a result, patients with CSD and migraine, postconcussional syndrome, or dysautonomia were included in otogenic and interactive CSD subgroups. Clinical experience and advances in treatment research argue for separating these medical illnesses into their own categories, as was done in the present investigation. This newer approach to the differential diagnosis of CSD ensures that both medical and psychiatric conditions associated with chronic dizziness will be identified appropriately.

The results of this investigation provide some insight into pathophysiologic mechanisms that may precipitate and perpetuate chronic dizziness. Two thirds of patients had medical conditions associated with the onset of dizziness, whereas one third had anxiety disorders as the initial cause. Therefore, CSD may be triggered by either neurotologic or psychiatric conditions. In the case of CSD with anxiety, the fact that patients were found to have no ongoing medical illnesses indicates quite strongly that psychological factors can sustain chronic dizziness, regardless of its initial cause. In this regard, other investigators\textsuperscript{16,17} have found acute dizziness to be a particularly potent trigger of anxiety, and acute anxiety in the face of new onset dizziness was the best predictor of chronic symptoms at 1 year after an episode of vestibular neuritis.

The prevalence of migraine headaches in this study was 18.8% for women and 12.0% for men, which was not much different than the prevailing rates of 17.2% for women and 6% for men in the geographical area from which this study population was drawn.\textsuperscript{19} In contrast, the rate of coexisting anxiety disorders in the migraine group (77%) was much higher than the combined rate of 18.1% for all anxiety disorders found in epidemiologic studies of the US population.\textsuperscript{20} This suggests that for patients with migraine and nonvertiginous dizziness, anxiety-related mechanisms may play a more significant role than headache-related processes in sustaining chronic symptoms. Of course, clinical experience suggests that patients with migraine-associated true vertigo, who were excluded from this study, may also have CSD-like symptoms between headaches.\textsuperscript{13,18} Therefore, future investigations will have to establish the precipitating and perpetuating mechanisms of chronic dizziness in migraineurs with vertiginous and nonvertiginous dizziness with or without comorbid anxiety.

The rate of TBI was 15.1% in this study cohort compared with approximately 0.6% in the general population.\textsuperscript{21} Thus, TBI was heavily overrepresented among patients with CSD, suggesting that concussive brain injuries and whiplash can cause persistent, nonvertiginous dizziness. In fact, CSD symptoms following TBI may carry a poor prognosis. In an otherwise healthy, highly motivated group of military service members who suffered concussions in blast injuries, recovery from CSD-like dizziness was far more prolonged than recovery from vertigo owing to direct labyrinthine trauma or posttraumatic vestibular migraine.\textsuperscript{6} The pathophysiologic mechanisms that cause CSD in patients with TBI are not known but are probably not related to anxiety, given the low rates of anxiety disorders found in the TBI group.

Reliable estimates of the prevalence of dysautonomias are not available. The combined rate of comorbid anxiety in the dysautonomia group (37.5%) was twice as high as the general US population, but most patients with dysautonomias in this study did not have anxiety disorders. This suggests that central nervous system mechanisms responsible for type 1 neurally mediated dysautonomia and postural orthostatic tachycardia syndrome operate independently of anxiety-related processes but may interact with them.

This study demonstrated the clinical usefulness of CSD as a diagnostic concept to identify patients with persistent dizziness sustained by nonotologic mechanisms. Several major causes of chronic nonvertiginous dizziness were identified, including anxiety disorders, migraine, TBI, and dysautonomias. High levels of coexisting anxiety frequently dominated the clinical picture and confounded recognition of associated medical illnesses. Key diagnostic features were identified in the clinical history for each illness. Careful inquiry about these key features during otologic evaluations may increase diagnostic precision and lead to more specific treatment recommendations for these perplexing patients.
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Author Contributions: Dr Staab had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Staab and Ruckenstein. Acquisition of data: Staab and Ruckenstein. Analysis and interpretation of data: Staab and Ruckenstein. Drafting of the manuscript: Staab and Ruckenstein. Critical revision of the manuscript for important intellectual content: Staab and Ruckenstein. Statistical analysis: Staab.

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REFERENCES