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What Investigations Are Ordered in Patients with First-episode Psychosis?

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ABSTRACT

Psychiatrists are often left with the dilemma of which investigations to order in adolescents presenting with a first episode of psychosis. Blood work, urine studies, and neuroimaging studies were tracked in 13 adolescents admitted with a diagnosis of first-episode psychosis over a 13-month period to the Children's Hospital of Eastern Ontario. Variation was found in the amount of investigation ordered: 85% of patients received a drug screen; 54% a CT scan; 8% an MRI; 92% a CBC with differential; 92% electrolytes. Abnormalities of CT scans were detected in 2 patients (29%); in neither case did the result lead to a diagnosis of brain-lesion-related psychosis, nor did it affect the clinical care of the patient. This study highlights the need to develop clinical practice-guidelines for the workup of first-episode psychosis in adolescents.

First-episode psychosis has received considerable attention in both the pediatric and adult literature. One area of ongoing research is the degree to which children and adolescents require investigations to rule in or rule out non-psychiatric disease. According to the Diagnostic and Statistical Manual of Mental Disorders 4th Edition Text Revision (DSM-IV-TR), the diagnosis of schizophrenia and other psychotic illnesses require that criteria be met: where "the disturbance is not due to the direct physiological effects of a substance (e.g., of abuse or a medication) or a general medical condition"(1). Yet, in spite of these essential criteria, a standardized work-up for first episode psychosis in children and youth is difficult to find.

Psychiatry associations and textbooks differ in their recommendations and often leave the decision to perform a test at the discretion of the attending physician. A summary of different guidelines can be found in Table 1.

Table 1: Summary of various guidelines for the investigation of patients with first episode psychosis

Source	Suggested Work-up
Kaplan and Sadock(2)	• Do: complete history and physical exam, urine toxicology screen, CBC, general chemistry screen, urinalysis • Consider: pregnancy test, ECG, MRI, CT, EEG
Rutter and Taylor(3)	• Do: CBC, ESR, electrolytes, renal function tests, glucose, calcium, magnesium, phosphate, liver enzymes, albumin, TSH, urinalysis, urine toxicology screen • Consider: neuroimaging
Wiener(4)	• Do: sexually transmitted disease screen • Consider other investigations as guided by history and physical exam
American Psychiatric Association(5)	• Do: history and physical exam, thyroid function tests, renal function tests, liver function tests, pregnancy screen, toxicology screen, syphilis screen • Consider: screening for HIV and hepatitis C, EEG/CT/MRI if indicated (new onset psychosis and atypical psychosis)
American Association of Child and Adolescent Psychiatrists (AACAP)(6, 7)	• Consider: CBC, chemistry, thyroid function tests, urinalysis, toxicology screen, infectious disease screens (if at risk)[+], chromosomal analysis (if suggestive of developmental syndrome), neuroimaging (if evidence of neurologic dysfunction)

CBC – complete blood count / ECG – electrocardiogram
MRI – magnetic resonance imaging / CT – computed Tomography
EEG – electroencephalogram / ESR – erythrocyte sedimentation rate
TSH – thyroid stimulating hormone
[+] - high risk groups include: all adolescents with psychiatric symptoms; high risk adolescents (e.g.: runaways, delinquents, children of substance abusers); adolescents with changes in mental status or performance; adolescents with acute behavior changes; adolescents with recurrent accidents or unexplained somatic symptoms; adolescents for whom abstinence is to be monitored

There is much debate in the literature regarding the inclusion of neuroimaging in the standard work-up of children with first-episode psychosis. Some advocate a rule-in approach while others prefer a rule-out approach. The AACAP suggests that the use of CT and MRI be reserved for ruling out intracranial disease when suspected, and that they are of very low positive yield in the absence of clinical findings.(6, 7) Adams et al. conclude that routine endocrine and neuroimaging screening tests in first-onset adolescent psychosis are of little diagnostic utility and are not cost effective (8). They recommend that investigations be reserved for cases with symptoms suggestive of non-psychiatric pathology. Larson et al. concluded that CT scans should be used to rule in intracranial pathology as it has low yield in assisting clinical decisions in the absence of focal neurologic deficit (9).

Yet a growing body of evidence suggests the potential value of neuroimaging for patients with first-episode psychosis. Various CT studies in adolescents and adults have found that patients with schizophrenia and other psychotic disorders exhibit ventricular enlargement, cortical atrophy, and cerebrospinal-fluid (CSF) circulation-disturbances (10-16). Magnetic resonance imaging is increasingly being used as a diagnostic and research tool in psychiatric illness. Various studies report gray matter deficits, increased CSF volume, decreased cerebral volume, thalamic abnormalities, and diminished size of the fusiform gyrus associated with psychosis (15-22). Jacobsen and Rapoport suggest that CT and MRI changes are not static but are affected by the duration or severity of illness and the modality and success of treatment (21).

Moreno et al. note that the interpretation of pediatric neuroimaging studies is difficult, owing to the variability of normal results secondary to age and body-size. They also note that diagnostic testing may be required in assisting patients and their families in gaining access to social and financial services (23).

Finally, many psychiatrists have informally reported cases of first-episode psychosis that have later been determined to result from a general medical condition (for example, intracranial tumor, developmental structural anomalies, metabolic disease, genetic disease, or seizure disorder). Thus, some psychiatrists advocate that a thorough workup should be done from a quality and risk management perspective. But few data, to date, support this perspective.

METHODS

All psychiatry inpatients admitted for the 13 months from October 1, 2000 to October 31, 2001 were eligible for entry into the study database. Patients or their legal guardians (for those under 16 years of age) gave consent for their inclusion. The Research Ethics Board of the Children's Hospital of Eastern Ontario (CHEO) approved the study.

Patients were excluded from this study if they had a seizure disorder, diabetes, anemia, migraine, endocrine disorder, or vitamin B12 deficiency. Patients readmitted to service were also excluded.

This process identified 174 patients, of which 13 presented with a primary diagnosis of psychosis. The remainder had mood or anxiety disorders. There were many more cases of psychosis, but they either presented with mood symptoms, or the psychosis was not evident at the time of admission. The 13 diagnosed with first-episode psychosis were age 14 to 17 years; 9 were male and 4 were female.

Research assistants reviewed all inpatient charts and records and biological data was entered into the study database. Laboratory results were collected for patients and were divided based on whether tests were normal, abnormal, abnormally high, abnormally low and not ordered. Percentages of normal and abnormal results were calculated based on the number of tests ordered. With the exception of the CBC and urinalysis, which are required by the hospital for all admitted patients, tests are ordered at the discretion of the admitting psychiatrist.

RESULTS

A neuroimaging study was ordered in 62% of patients (Table 2). Of these 8 studies, an abnormality was detected in 2.

Table 2: Results of neuroimaging studies for children and adolescents admitted to the Children's Hospital of Eastern Ontario with a diagnosis of first-episode psychosis

Test	Norm	Abnorm	Not Ordered
CT Head	5	2	6
MRI	1	0	12
EEG	8	0	5

With respect to blood tests and urine toxicology, 92% of the patients were investigated (Tables 3 and 4).

Table 3: Laboratory investigations performed in 13 patients admitted to the Children's Hospital of Eastern Ontario with a diagnosis of first-episode psychosis

Test	Normal	Abnormal high	Abnormal low	Not Ordered
WBC	8	2	2	1
Neutrophils	9	2	1	1
Hemoglobin	10	1	1	1
Platelets	12	0	0	1
TSH	11	0	0	2
AST	7	0	0	6
ALT	8	1	3	1
Sodium	12	0	0	1
Chloride	12	0	0	1
Potassium	12	0	0	1
Calcium	0	0	0	13
Magnesium	5	0	0	8
Phosphate	5	0	0	8
Glucose	5	1	2	5
Urea	8	0	2	3
Creatinine	10	1	0	2

Table 4: Toxin and drug of abuse testing in a sample of children and adolescents admitted to the Children's Hospital of Eastern Ontario with a diagnosis of first-episode psychosis

Toxin Screened	**Negative**	**Positive**	**Not ordered**
Acetaminophen	0	2	11
Salicylates	0	2	11
Ethanol	1	0	12
Phencyclidine	11	0	2
Benzodiazepines	8	3	2
Cocaine	11	0	2
Amphetamines	10	1	2
Tetrahydrocannabinol	7	4	2
Opiates	10	1	2
Barbiturates	11	0	2

No patients were tested for sexually transmitted diseases. Two of the four female patients were tested for pregnancy. Both tests were negative.

DISCUSSION

There is considerable variation in investigations ordered by admitting psychiatrists for the workup of first-episode psychosis. Psychiatrists, overall, at the Children's Hospital of Eastern Ontario tended to order more tests than are recommended by some authors, but vary greatly among themselves: 85% of patients received a drug screen, 54% received a CT scan, 8% received an MRI and 92% received a CBC with differential and electrolytes. The variability may result from the lack of a clear practice guideline from an authoritative source or the risks, both medical and legal, of missing an alternative diagnosis. Some sources suggest the variability results from the lack of confidence psychiatrists have in their medical knowledge (8).

Attention should be given to differentiating which tests should be used for screening purposes and which tests for diagnostic purposes. In our study, 29% of patients who received a CT scan of the head had an abnormal result. One patient had a questionable mass in the right frontal lobe (not confirmed by MRI). The other abnormal CT was suggestive of slightly large ventricles; MRI investigation was not done on this patient during the study period. Neither abnormal CT result impacted on the patient's diagnosis or treatment. As MRI becomes more accessible and affordable in Canada and a better understanding of the relationship between clinical and neuroimaging findings is attained, MRI may prove to be of utility in the clinical investigation of psychosis. This is also true of newer modalities such as positron emission tomography and single photon emission tomography.

It is widely understood that substance use is common in individuals with psychosis**.** Our study found that a considerable percentage of our subjects had clinically detectable levels of substances in their bodies. Of greater concern, however, is that 15% of patients were not screened for any substances at all, and 92% were not screened for ethanol. Given that substances can cause psychosis, affect its prognosis, and represent a major comorbidity, it seems essential that these particular investigations be considered in all patients with a psychotic presentation.

Limitations of this study are clear. Our sample size is small, and correlative and causative conclusions cannot be drawn. We did not capture why certain studies were ordered in some patients and not others. Finally, the study was limited to biological investigations, and does not include the potentially valuable contribution of psychological and other evaluations.

Based on the results of this study, we can conclude that there is large variability in the ordering of investigations at CHEO for adolescents with first-episode psychosis. The findings of abnormal CT scans correlate with previous studies. Correlative and causative conclusions cannot be drawn with such a small sample

size. Therefore, more studies are needed to better standardize admission investigations and determine clinical correlations with laboratory findings. This will help guide further investigations such as cost/benefit analysis and monitoring of disease and treatment response.

SOURCE INFORMATION

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Psychogenic Stuttering Following a Gastric Bypass Operation: Case Report

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ABSTRACT

We evaluated a 44-year-old female with bipolar affective disorder who presented with a 4-month history of severe stuttering and vague neurologic complaints. She had lost 200 pounds after gastric bypass surgery two years before. A childhood sexual- abuse victim, she admits that she "hid" in her weight for most of her life. Neurological evaluation of this patient was negative, and speech-pathology evaluation revealed highly atypical stuttering. Gastric bypass patients with a history of psychiatric disorders and childhood sexual abuse may be particularly vulnerable to somatoform disorders.

It has been widely reported that psychological complications are prevalent among the morbidly obese, although this point has been controversial (1). Glinski et al. elucidated that 70% of patients evaluated for gastric bypass surgery meet criteria for an Axis I disorder in the past or present and 36% for Axis II disorder (2). In his study, he found that the lifetime prevalence of depressive disorders alone in this population was 56%, compared with the known lifetime prevalence of depressive disorders of about 17% in the general population. Glinski noted that gastric bypass surgical candidates tend to use denial as a defense mechanism for avoiding negative emotions. In keeping with this, overeating may serve as distraction from negative emotion in these individuals. Somatization is another tendency in this particular population.

Some improvement of psychosocial functioning after surgical treatment of obesity has been reported (3). Van Gemert et al. recently investigated the long-term effects of surgically induced weight loss on the psychological functioning of morbidly obese patients. They found that preoperative subjects had elevated values on negativism, somatization, and shyness scales on personality profiles; postoperatively, all these values normalized except somatization. Thus, postoperative patients still were concerned about their health and still were inclined to react to psychological stress with physical complaints.

Interestingly, Waters et al. found that the dramatic improvement in those mental health indices observed 6 and 12 months after gastric bypass surgery tends to erode to preoperative values two years after surgery, despite no weight gain (4). As a possible explanation for this psychological regression, Waters's group noted that for the first 12 postoperative months, patients have frequent clinic visits that taper off over the second year: continued psychological support may remain essential for patients after bariatric surgery. Moreover, patients with previously diagnosed Axis I disorders may require more support than those without. When Halmi et al. evaluated 80 morbidly obese patients after gastric bypass, they found that those patients with documented psychiatric diagnoses had a significantly greater amount of psychosocial stress than those without those diagnoses (1).

Impact of Past Sexual Abuse on Obesity and Outcome after Gastric Bypass

Sexually abused women are more likely than nonabused women to receive a psychiatric diagnosis during their lifetimes (5). Women with a history of sexual abuse are also more likely to experience somatically based stress disorders and somatic disorders in general (6). Moreover, multiple studies have found a relationship between childhood sexual abuse and extreme obesity. Associations between childhood physical abuse and obesity, as well as between childhood neglect and obesity, also have been found (7), but core psychological reasons may differ.

A chart review of 131 patients by Gustafson et al. revealed that 60% of those who reported a history of sexual abuse were more than 50 pounds overweight, compared with 28% of age-and-sex-matched patients without a history of sexual abuse (5). In addition, 25% of the abused group was found to be more than 100 pounds overweight, compared with only 6% of controls. Researchers have proposed that the obesity may serve as protection from sexual advances from potential abusers. Wiederman et al. showed that among obese women, those with a history of sexual abuse reported less body dissatisfaction and less weight fluctuation during adulthood compared with obese women who were not sexually abused, indicating that excess weight likely serves a particular function in sexual abuse victims (8). Moreover, King, et al found in an outpatient weight-management program that research subjects with a history of sexual abuse lost significantly less weight than those with no history of abuse (9). It has been suggested that weight reduction in these patients may trigger anxiety symptoms as women approach the weight at which they were abused (5, 9).

Researchers have examined the correlation between sexual abuse history and weight-loss treatment failure. In general, childhood sexual abuse survivors are less likely to be successful in maintaining weight loss after obesity treatment (10).

King et al. showed that obese individuals with a history of sexual abuse were more likely to have experienced psychological distress and to have lower self efficacy than their counterparts who were not abused, making compliance with an obesity treatment program exceedingly difficult in comparison. It follows that a history of sexual abuse is an important pretreatment variable that may have a significant impact on obesity treatment outcome (9). Although Buser et al. showed in their study that females with a history of sexual abuse were as successful with weight loss for the first 14 months after gastric bypass surgery as those without a history of sexual abuse, they do validate the necessity of additional support during and after weight loss interventions for individuals with a history of sexual abuse (11).

Psychogenic stuttering

Stuttering is generally categorized as developmental or acquired. Adult-onset stuttering is either a reemergence of a childhood (developmental) stutter or acquired, either neurogenic or psychogenic in nature. The mechanism of developmental stuttering still is not well-understood: impaired neuronal communication, disturbed timing of activation in speech-relevant brain areas, and neuroanatomical abnormalities in the speech-language areas all have been implicated (12, 13). Neurogenic causes of acquired stuttering include head injury, stroke, degenerative disease of the central nervous system, brain tumor, brain-surgery, defects in the basal nuclei or thalamus, and drug-induced brain dysfunctions (14, 15). In a case series by Roth, et al. involving 12 subjects with adult-onset stuttering that turned out to be psychogenic in nature, all initially required differentiation of neurologic from psychogenic stuttering through interdisciplinary collaboration. All 12 subjects with psychogenic stuttering presented with other, concomitant neurologic-like complaints which also turned out to be nonorganic in etiology (16).

Psychogenic stuttering is well-described (15). The term “conversion reaction,” which refers to a process, through which psychological stress is converted into a somatic symptom, largely has replaced the older term “hysteria.” Psychogenic stuttering, once known as “hysterical stuttering,” currently is considered a conversion disorder: an alteration in physical functioning that suggests a physical disorder but is an expression of psychological conflict (15).

The sudden onset of psychogenic stuttering is commonly preceded by an emotionally traumatizing event. Ten of the twelve patients that comprised Roth’s aforementioned case series had significant psychological disturbances surrounding the onset and development of the stuttering; the remaining two subjects were equivocal in this regard (16). Mahr and Leith recently described a woman with an abuse history who was struggling with her decision to leave her husband when she

suddenly began to stutter (15). Deal has suggested that adult-onset non-developmental and non-neurologically based stuttering usually has a sudden onset and is temporally linked to some form of psychological trauma or cumulative psychological stress (17). He reported an adult patient who had two discrete episodes of sudden-onset stuttering, each after an unsuccessful suicide attempt.

Mahr and Leith have presented a clear synthesis of the most up-to-date diagnostic schemes for psychogenic stuttering. *Defining criteria* 1. a change in speech pattern suggesting stut-tering; 2. a relationship to psychological factors; 3. absence of organic cause. *Associated symptoms* 1. history of mental illness; 2. atypical features of stuttering, such as no secondary symptoms and no islands of fluency; 3. *la belle indifference*. These authors have proposed that for stuttering to be diagnosed as a conversion reaction, all defining criteria must be met in addition to one associated symptom (15).

As opposed to developmental stuttering, for which studies have demonstrated a 1:3 female:male ratio, psychogenic stuttering has been shown to occur in a 1:1 female: male ratio (14).

CASE REPORT

Ms. S is a 44-year-old Caucasian female who, two years after Roux-en-Y gastric bypass for morbid obesity, presented to us with a 4-month history of severe stuttering. Neurologic symptoms were present also, which had been intermittent over the last year but worse over the last four months. As a result of symptoms, she had stopped working. Bipolar affective disorder had been diagnosed 15 years earlier, and, in addition, she reported childhood sexual abuse.

Ms. S has been hospitalized several times for bipolar illness. One admission was for feeling "low" after separation from her first husband; another was for adjustment of her psychiatric medications. Lithium had caused a "toxic reaction," valproic acid gave her "decreased touch sensation," then carbamazepine was started without adverse effect. More recently, low dose quetiapine was also initiated. Of note, stuttering began prior to the initiation of quetiapine. This patient has no history of substance abuse.

Past medical history is significant for obesity, which worsened after the births of her three children in her early twenties. Tubal ligation was carried out in her late twenties. The gastric bypass-operation mentioned above was accompanied by open cholecystectomy.

Ms. S was thin as a child, but gained weight at puberty: she was afraid to be around boys, and her developing body triggered memories of sexual abuse at age three by her father. In her adolescence she avoided boys and tried to "hide" in her weight. "A lot of therapy" over the years helped her deal with her childhood sexual abuse until she reached a point where she no longer psychologically "needed" the weight.

She has a Bachelor's Degree, has completed graduate-level coursework, and has been employed in the field of career-development. She married in her early twenties and felt supported by her husband, although the intimate nature of their relationship was limited. Her three children, with whom she has a close relationship, are from this marriage. After 20 years of marriage, Ms. S and her first husband divorced, owing to his involvement with other women. Following the divorce, Ms. S proceeded with gastric bypass, which resulted in a loss of 200 pounds. Over the next year, she found herself to enjoy dating, which involved physical intimacy with men. About one year ago, she married her current husband, whom she describes as supportive, and with whom she is frequently physically intimate. She does report that her new husband has told her that he likely would not have taken interest in her had she been overweight when they first met.

Two siblings suffer from a mood disorder and from substance abuse; alcoholism has been present in both parents. Her father died from a brain tumor, and her grandfather had Parkinson's disease.

She is pleasant and friendly, stuttering on many of her words. She does not "mind the stuttering" and says with a smile that she "would not want to associate with people who would take issue with it anyway." She reports an active social life and has been initiating conversation with new people without self-consciousness. Her "flippers," which she calls her minimal bilateral arm fat, seem to be of more concern to her than is the stuttering. However, she does report that stuttering and occasional double vision interfere with her ability to work because she could not answer phones effectively or drive safely. As she describes matters, she has become highly dependent on her husband and her children to drive her to numerous medical appointments that now occupy much of her time.

Affect is labile during interviews; she is tearful when speaking about her bipolar disorder and the inability of medications to "fix it." Throughout her life, she has felt that care providers have not believed her regarding her mood symptoms. This has frustrated her; she compares it to times in her childhood when her mother would not believe she was sick unless there was objective evidence, such as a fever. The patient cites low self-esteem as her biggest lifelong psychological problem, often feeling that she is "a bother" to people, particularly when she has depressed mood. She worries that her new husband may leave her, and she fears

gaining weight because “looks” are very important to him. Even so, things have been going well in the last year: a generally supportive marriage and a rewarding, albeit stressful, job. Ms. S has been told that her stuttering may be related to “anxiety,” but is confused because stress level has been much higher in other times of her life. Stuttering has never existed in the past. Moreover, she asserts, the only person she has ever known who stuttered is a character on a television program that she used to watch often.

She is unable to recount the details around the sudden onset of stuttering, but recalls that it started at the end of a vacation with her husband about one month prior to termination with her therapist of eight years; the latter was moving across the country. Ms. S now states that were she to stop stuttering, she might “miss it,” because it has become part of her “identity.” She does not believe that she has received more attention since the stuttering began. She has stopped working, going on disability and enjoying her new status as a “domestic engineer.”

Extensive neurological workup was carried out for the following complaints: stuttering, continuous for 4 months, of sudden onset; double vision, about 20 percent of the time, for 4 months; hand tremor, at rest, for one week; and memory and attention difficulties over the past month. Tremor was not observed during serial physical examinations, and unsteadiness with tandem gait and difficulty with balance were present on some occasions but not others; finger-nose-finger and heel-to-shin exercises were within normal limits. In sum, physical findings were inconsistent and elaborated. A thorough ophthalmic evaluation showed no abnormalities. MRA and MRI imaging was unremarkable, and testing was negative for infectious, endocrinologic, metabolic, and rheumatologic processes.

Speech evaluation revealed a moderate to severe dysfluency in about 50 percent of all spoken words, persisting when reading slowly. Certain behaviors were missing that normally accompany dysfluencies in adults: prolongations of sounds and secondary mannerisms (increased facial muscle or laryngeal tension). Neither discontinuation of quetiapine nor reduction in the dose of carabamazepine improved the patient’s symptoms.

When the symptoms initially arose, Ms. S had begun to schedule more medical and psychiatry appointments; this was shortly before termination with her therapist of eight years. Since, she has seen psychiatrists at more than one facility and has sought multiple primary care visits. Chief complaints vary; one such is that of urinary symptoms (but they are unaccompanied by evidence of infection). Weekly psychotherapy sessions were initiated at our institution, but her care soon was transferred to a facility closer to her home.

DISCUSSION

Neurologic complications of bariatric surgical procedures do occur, neuropathy, encephalopathy, vitamin B12 deficiency, and thiamine deficiency, for example (18). Although we found no evidence of an organic basis for our patient's symptoms, we did find from speech and psychological evaluations that, in addition to *la belle indifference*, nearly every criterion (see above) of Mahr and Leith for psychogenic stuttering was present. And multiple and vague quasi-neurologic symptoms accompanied the complaint of stuttering, just as Roth observed in all twelve of his psychogenic-stuttering subjects (16).

Accepting the diagnosis of a conversion reaction in this patient, what unconscious psychological conflict does Ms. S express through her stuttering? A number of possibilities exist. A therapist of eight years recently moved away. This abrupt termination took place alongside the recent, steady diminution of this patient's medical appointments since the bariatric operation, cutting her contact with care providers significantly. As mentioned, Waters has noted an erosion of mental health about two years after gastric bypass surgery (4). This also is when some patients tend to regain weight. Ms. S fears gaining weight because she worries that her husband will leave her if she becomes obese. On the other hand, as a sexual abuse survivor, without the protection of obesity she may be especially vulnerable to unconscious fear (9). Somatic symptoms produce the nurturing care, the protection, of family and healthcare workers. She can cite many instances in her life when she has tried to communicate her needs and has not been believed; stuttering is noticeable; it demands attention. And, given the involvement of the oral cavity in stuttering, one might wonder if the symptom represents a displacement of guilt or fantasy about either oral sex or eating. These would be topics to further explore in dynamically oriented psychotherapy.

Could the emergence of Ms. S's somatic symptoms have been prevented? A history existed of both bipolar affective disorder and childhood sexual abuse: one could argue that she was predisposed to psychological deterioration after her identity-altering surgery. According to both Waters and Buser, additional and continued psychological support should be offered to patients following bariatric operations, particularly those with a history of a psychiatric disorder and a history of childhood sexual abuse (4, 11).

SOURCE INFORMATION

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Psychiatric Diagnoses in Patients with Williams Syndrome and Their Families

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ABSTRACT

Williams Syndrome (WS) is a genetic disorder associated with mental retardation (MR) and a distinct behavioral phenotype including a friendly and outgoing personality. This population, like others with MR, has been reported to have an increased rate of symptoms of mental illness; however, few studies have used DSM-IV criteria to quantify specific psychiatric diagnoses in WS and the prevalence of psychiatric illness in relatives of individuals with WS and the possible relationship between family and patient diagnoses is currently unknown.

Methods: **Twenty-one families participated; the patients' average age was 16 years. DSM-IV diagnoses were applied by using the Anxiety Disorders Interview Schedule (ADIS, Parent and Child Versions) and the Family History Screen.**

Results: **A diagnosis from the ADIS was applicable to 13 patients (62%), and in 16 patients (76%) a diagnosis was applicable in their first-degree family members. Ten patients (48%) had some form of anxiety, specific phobia being the most common. Three patients (14%) had major depressive disorder and 9 patients (43%) had attention-deficit/hyperactivity disorder (ADHD). The presence of anxiety or mood disorders in patients with WS and the presence of these disorders in their family members were unrelated.**

Conclusions: **Patients with WS have a high prevalence of anxiety disorders and of ADHD. The presence of psychiatric disorders in WS did not appear to have a significant relationship to family history of psychiatric disorders, consistent with *the hypothesis that the specific genetic alteration in WS causes, or contributes to causing, the anxiety disorders and the ADHD that are so common in the disorder*.**

Populations with mental retardation (MR), especially those with known genetic alterations, offer a window into the effects of genes on determining cognition and behavior. Populations with MR are known to have increased rates of emotional distress and mental illness (1, 2). While estimates vary, the prevalence of

psychiatric disorders in individuals with MR is reported as three to four times than in the general population (3). Of children with MR living in the community, 20-35% have been found to have a comorbid mental illness (2). Reported rates of psychiatric diagnoses in this population have varied, ranging from 12% to 42% (2). More recent studies demonstrate the prevalence of psychiatric disorders in MR children to be 33-40% (4, 5). When DSM-IV criteria are used, 39% of a cohort of mentally retarded children have a diagnosable mental illness (6)

Williams syndrome (WS) serves as a prototype for studying the relationship between genetics and behavior because affected patients have a strikingly similar behavioral phenotype. WS results from a deletion that includes the elastin gene on chromosome 7q11.23 and occurs in 1 in 10,000-20,000 births (7, 8). Most cases result from a new mutation. The associated mental retardation generally results in an IQ between 41 and 80 (8). Other characteristics of WS include short stature, specific facial features, hyperacusis, and cardiovascular defects. Individuals with WS demonstrate relative strengths in auditory rote memory and verbal ability. Compared to other mentally retarded individuals with similar IQ, children with WS speak more fluently, possess larger vocabularies, and are better conversationalists (8). Additionally, these patients are highly sociable, an affability sometimes described as a "cocktail party personality": talkative, overfriendly, and outgoing; they notably lack stranger anxiety.

Individuals with WS frequently exhibit psychiatric symptoms: generalized anxiety and worries, negative mood, and sensitivity to criticism. Behavioral and emotional disturbances have been reported in up to 80% of children with WS, much higher than in other mentally retarded populations (9). They have significantly more fears as well as a wider range of frequently occurring fears as compared to other mentally retarded populations, and also have an increased prevalence of anticipatory anxiety (10).

Even so, few studies have used DSM-IV criteria to quantify specific psychiatric diagnoses. Additionally, there is little research examining the possible relationship between family history of psychiatric illness and psychiatric diagnoses in WS patients. This study aims to identify the prevalence and nature of psychiatric disorders in patients with WS using standard DSM-IV criteria. The study also aims to determine the prevalence of psychiatric disorders in first-degree relatives of WS patients and examine the possible relationship between family history of psychiatric illness and patient symptomatology. We hypothesized that if mood, anxiety, or ADHD disorders were a part of the WS behavioral phenotype in and of itself, there would be no relationship between the presence of those disorders in patients and their presence in family members.

METHODS

All patients age 7 years or older who have been evaluated at the Williams Syndrome Clinic of Women and Children's Hospital of Buffalo, NY were contacted by mail and telephone to participate in the study. The Williams Syndrome Clinic is a multidisciplinary center that regularly evaluates patients from a large geographic area. Patients were excluded from the study if a biological parent was not the primary caregiver. Twenty-one of 28 eligible families agreed to participate. All were Caucasian. All children with WS lived at home with one or both parents. They ranged in age from 7-28 years (mean 16 years); 14 of the 21 patients were female. All patients had WS that was confirmed by fluorescence *in situ* hybridization (FISH) analysis. Seven patients had currently or previously taken one or more pharmacologic agents for treatment of psychiatric or behavioral symptoms.

Patients and both parents, when available, were interviewed in their own homes by a single examiner (JCK). Seventeen families (81%) had both parents present at the time of interview. Subjects and parents received information on the nature of the study and the assessment tools; subjects and the parents that were present gave written informed consent. The study methods were approved by the Institutional Review Board of Women and Children's Hospital of Buffalo. Parent and child responses and diagnoses were reviewed by a child and adolescent psychiatrist (DLK).

Measurements

The Anxiety Disorders Interview Schedule (ADIS) is a standardized semi-structured interview that uses DSM-IV criteria to assess for 14 psychiatric disorders in children and adolescents, including anxiety, specific phobia, MDD, and ADHD (11). The ADIS was administered separately to the parents and the individual with WS (using both Parent and Child Versions) to arrive at a single combined score. In order for a diagnosis to be assigned, symptom-criteria must be met and must interfere with functioning. An impairment in functioning is defined by a minimum score of 4 on a scale of 0 to 8, as rated by both the subject and the parents in answer to the questions: "How much has [the problem] messed things up for you with friends, in school, or at home? How much does it stop you from doing things you would like to do?"

The Family History Screen (FHS) is a semi-structured interview assessing lifetime history for 15 psychiatric disorders in subjects and first-degree relatives (parents and siblings) (12). The FHS was administered separately to each

biological parent. Diagnoses queried included anxiety, specific phobia, MDD, and ADHD.

Data Analysis

Descriptive analyses were used for the prevalence and distribution of psychiatric diagnoses in the study population. The association between patient and family history of selected disorders was analyzed using Fisher's exact tests for contingency tables. Disorders examined in subjects and family members were MDD, any anxiety, specific phobia, and ADHD, as these were expected to be the most prevalent based on previous studies (1, 13). Because anxiety and depression may occur together, analyses were also performed for any mood *or* anxiety disorder. Fisher's exact test was chosen over the Chi-square test for independence because of the small cell- frequencies (expected cell frequencies ≤ 5) in all of the 2x2 contingency tables. For Fisher's exact test, the null hypotheses of independence was performed at a 0.05 significance level. All of the statistical analyses are performed on SAS version-9.

RESULTS

DSM-IV Diagnoses in WS population

Thirteen of 21 subjects (62%) had at least one DSM-IV diagnosis (Table 1). The most common were: any anxiety disorder (48%), specific phobia (43%), ADHD (43%), and generalized anxiety disorder (GAD) (24%). Major depressive disorder (MDD) was found in 3/21 (14%) of the patients. There were no significant differences with regard to sex or age for any diagnosis. More than one diagnosis was present in 33% of the sample; 24% had more than 2 diagnoses.

Phobias. Specific phobia was present in 43% of patients and was the most common type of anxiety disorder, present in 9 of the 10 subjects with an anxiety diagnosis. The most common types of specific phobia were animal, thunderstorm/lightning, and loud noises. Seven of the 9 patients had multiple phobias. No subject had social phobia.

ADHD. Of the subjects with ADHD, 8 of 9 were of the inattentive type, 1 was the combined type, and none were of the hyperactive-impulsive subtype.

ADIS diagnosis requires a functional interference score greater than 4 out of 8. Many more of these subjects met a symptom-criteria for diagnosis but did not meet the requirement for functional interference. Fifteen subjects (71%) demonstrated symptoms of specific phobia but only 9 (43%) had significant impairment in

functioning. Two additional subjects met criteria for GAD, and 4 additional subjects met criteria for ADHD but again did not meet the functional interference requirement.

Table I. Diagnoses in Williams Syndrome Patients

Diagnosis	*n*	%
Any Diagnosis	13	62
Any Anxiety Disorder	10	48
Separation Anxiety	1	5
Social Phobia	0	0
Specific Phobia	9	43
Panic Disorder	1	5
Agoraphobia	1	5
Generalized Anxiety Disorder	5	24
Obsessive-Compulsive Disorder	0	0
Post Traumatic Stress Disorder	1	5
Dysthymia	2	10
Major Depressive Disorder	3	14
Any ADHD	9	43
ADHD-Inattentive	8	38
ADHD-Impulsive	0	0
ADHD-Combined	1	5
Conduct Disorder	0	0
Oppositional Defiant Disorder	1	5

Family History of Psychiatric Diagnoses

Seventy-six percent of subjects had first-degree relatives with any diagnosis on the FHS. The ADIS diagnoses used in statistical analysis were: MDD, any

anxiety, specific phobia, and ADHD. Variables examined were: presence or absence of a diagnosis in the subject, and presence or absence of the diagnosis in first-degree relatives.

Of the WS subjects with MDD, 2 of 3 had a first-degree family history of MDD; of those without MDD, 6/18 had a first-degree family history of MDD. There was no statistically significant association between family history of MDD and subject MDD ($p = 0.5308$).

Of the WS subjects with any anxiety diagnosis, 4/10 had a first-degree family history of anxiety; of subjects with no anxiety diagnosis, 6/11 had a first-degree family history of anxiety. There was no statistically significant association between family history of anxiety and subject anxiety ($p = 0.6699$).

Of the WS subjects with a mood *or* anxiety disorder, 6/11 had a first-degree family history of a mood or anxiety disorder; 7/10 subjects without a mood or anxiety disorder had a first-degree family history of a mood or anxiety disorder. There was no statistically significant association between family history of mood or anxiety disorders and subject mood or anxiety disorders ($p = 0.6594$).

No WS subject with specific phobia had a family history of specific phobia (0/9). Two subjects out of 12 with no diagnosis of phobia had a family history of specific phobia. There was no statistically significant association between first-degree family history of specific phobia and subject specific phobia (p-value = 0.4857).

Of the subjects with ADHD, 2/9 had a first-degree family history of ADHD; 1/12 without ADHD had a first-degree family history of ADHD. There was no statistically significant association between family ADHD and subject ADHD (p-value = 0.5534).

In summary, no statistically significant association was found between family history of MDD, any anxiety, specific phobia, and ADHD and the presence of these disorders in WS subjects.

DISCUSSION

The WS patients of this report have a higher prevalence of psychiatric disorders compared with other populations of MR children and adults (62% vs. 39%) (6), as well as compared with cognitively normal children (62% vs. 12%) (14). An increased prevalence of psychiatric diagnoses was observed even when impairment in functioning was required for diagnosis. The rates for specific diagnoses would have been higher if not for this requirement (e.g., 71% vs. 43% for specific phobia). The use of impairment in functioning is a distinctive aspect of this study and rarely has been used in previous studies.

Anxiety was the most prevalent diagnosis in the study population: 10/21 patients (48%). Five of these patients (24%) had GAD while 9 of 10 (43%) met diagnostic criteria for specific phobia. Types of phobias included animals, thunderstorms, loud noises, and high places. While some phobias may be attributed to the hyperacusis described in WS, not all phobias were related to sound. Most patients with phobias to loud noises also had phobias that were not sound-related. Despite the frequent occurrence of phobias, no patient had social phobia, consistent with the hypersociability that characterizes WS. This strong desire for social interaction appears to be an exception to the other anxieties observed in WS patients.

Previous studies of anxiety in WS have yielded similar results. Dykens reported excessive worry in 57% of children and adults with WS (10). However, using a DSM-III-R parent interview, only 16% of patients met diagnostic criteria for GAD, similar to the 24% observed in this study. Similarly, while 96% of patients reported persistent anxiety-producing fears, only 35% met diagnostic criteria for specific phobia (10). A multisystem study of WS adults that used the ADIS reported anxiety disorders in 65% of patients, with specific phobia being the most common subtype of anxiety (15). The present study further supports that anxiety disorders, especially specific phobia, appear to be distinctive behavioral findings in patients with WS. Of interest, despite frequent preoccupations in patients with WS, no patient met DSM-IV criteria for obsessive-compulsive disorder.

Nine patients (43%) met criteria for ADHD, with 8 of the 9 having the inattentive type. This is higher than rates reported in studies of other MR populations (4-21%) (1,13). Features of inattention and distractibility have previously been described in WS (16). Distinguishing ADHD from other features of mental retardation is, admittedly, difficult. For example, it may be that the hyperacusis in WS or some other attribute of MR contributes to distractibility. Alternatively, it may be that inattention is part of the behavioral phenotype of WS.

Only three patients (14%) were found to have a history of MDD. This appears consistent with estimates in the normal pediatric population of 8-20% (17) and in other studies of MR children of 4-10% (1).

Previous studies have not assessed the prevalence of psychiatric disorders in relatives of WS patients. Although psychiatric illness was common in first-degree relatives of the patients of this study (76% with any diagnosis), comparison of specific diagnoses between patients and relatives failed to yield a statistically significant association for any diagnosis. The data were analyzed to detect any relationship between the presence or absence of specific psychiatric disorders in family members and the presence or absence of each disorder in the WS patient. The absence of any significant relationship with family history is consistent with

our hypothesis that the presence of psychiatric illness in WS may be caused by the specific chromosomal deletion rather than the genetic contribution implicit in the family history of psychiatric illness. However, the statistical analyses performed were limited due to the small frequencies of the outcome measurements. Extrapolation of the data from the Fisher's exact test indicates that at least 60 subjects would be needed to find a statistically significant relationship among the variables. Therefore, while the results are suggestive that there may be a chromosomal link between psychiatric illness and WS, the data are insufficient to prove this conclusion.

Additional study limitations should be mentioned. As in any clinical research, it is important to acknowledge the possibility of non-response bias, specifically in this study that the families who agreed to participate may have had a different incidence of psychiatric disorders compared with those who declined. Additionally, there is an inherent recall bias in that families may under or over-report psychiatric illness in their family members in the presence of the interviewer. Findings could be enhanced in future studies by using a comparison group in the study itself, such as other MR populations. This would have been valuable because this study included the investigation of family history of psychiatric illness as well as the use of strict DSM-IV criteria in subjects, features not extensively investigated previously and therefore difficult to use in comparison analysis.

An important implication of this study is that greater attention needs to be devoted to recognizing psychiatric problems in individuals with MR, especially those with WS. Clinicians need to recognize the increased prevalence of specific disorders and to monitor for these illnesses as part of routine medical care, especially GAD, specific phobia, and ADHD. The psychiatric findings in patients with WS may provide insight into the genetic determinants of behavior and psychiatric illness in more generalized populations; therefore, additional research should continue to further investigate these relationships. Future research is also needed to systematically evaluate different treatments for anxiety disorders and ADHD in WS and other MR populations.

SOURCE INFORMATION

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No More Cuts: The Curious Fate of Self-Mutilation in Its Development

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ABSTRACT

In this article, we present descriptions of four young women with relatively severe personality disorders. All four were in psychodynamic psychotherapy and all had the symptom of self-cutting. During their treatment, it became evident that their self-cutting had undergone a transformation and a new symptom had appeared in its place. In three, self-cutting was substituted by behaviors that we might call "cutting equivalents" and, in the fourth, by an enhanced self-reflective attitude and by journal-writing. We suggest that symptom-replacement for self-cutting may be common in its developmental course or in its course as it becomes influenced by psychotherapy, and that the replacement is sometimes, perhaps often, salutary.

Approaching severe personality disorders psychodynamically has its pros and cons (1-3). On the one hand, it provides a deeper and more specific understanding of the patient, one in which his or her symptoms are seen as intricately bound with constitutional givens, early childhood experiences, and unconscious fantasies. On the other hand, if symptoms are end-products of a 'trauma-fantasy-wish-defense' sequence, any effort aimed simply at symptom-reduction is conceptually suspect and has practical risk. Psychodynamic models of etiology compel the prediction that removing a manifest disturbance might be undesirable, if the underlying issues responsible for it remain unresolved. This consideration acquires greater significance in cases of severe personality disorders (e.g., borderline, schizoid, antisocial, paranoid), which in some instances appear nearly intractable. The best outcome could be that a new, less toxic symptom replaces the older, more toxic one. Of course, if the former takes sublimatory or even "pseudo-sublimatory" form (1), the outcome can be regarded as not bad after all.

CASE REPORTS

Case 1

Inez is a 24-year-old nursing student with a history of self-cutting that began at age sixteen, dwindled around age eighteen, and stopped completely by age twenty-one. The onset of cutting coincided with her family's moving in with her new step-father. Inez felt she never belonged in that house and was like an unwanted guest. She cut herself when the feeling of being unwanted mounted and became unbearable. The urge to cut was more frequent, but she was able to restrict the act to once a month for fear of getting caught.

Inez was born to adolescent parents of different racial origins who were forced into a marriage because of the pregnancy. Inez's mother soon began an extramarital affair with a man who would later became Inez's stepfather; the parents divorced when she was twelve. Inez was aware of the infidelity, for her mother often had taken her to the house of the mother's lover before the divorce. She often had told Inez, from the latter's early childhood, that Inez was unwanted and the cause of her mother's unhappiness. Whenever they were separated, Inez found herself afraid that her mother would never return.

Inez began to work in a tattoo parlor at age eighteen. As an employee, she was able to get tattoos for free and often took advantage of this perk. Although she said that the pain of the needles bothered her, she found great pleasure in receiving the tattoos. She discovered even more pleasure in displaying them on her body. Interestingly, the self-cutting decreased soon after she began working in the tattoo parlor. Within two years, she had stopped cutting herself altogether, although she continued to obtain new tattoos regularly.

Case 2

Emily is a 23-year-old graduate student with a history of self-cutting that began at the age of fourteen and ended at eighteen. She began cutting herself soon after the onset of her menses, which she experienced as traumatic. Mostly she cut on her arms and forearms, but after her cutting was discovered by her friends she began cutting on her belly and thighs instead. Cutting relieved the tension that would follow on an argument with her mother. During childhood and adolescence Emily believed that her mother did not love her. Frequent, heated arguments took place, during which Emily would tell her mother that she hated her.

Emily had been born into a working class Catholic family that had traditional views regarding household gender-roles. Beginning at age ten, she was expected to begin preparing dinner before her parents came home; two older brothers had no such responsibilities. Because of this difference in treatment, she often felt that her

mother did not love her as much as she loved her brothers. She did not want to grow up to be a woman. Menarche was quite disturbing to her and was soon followed by the onset of self-cutting.

The cessation of cutting at eighteen seemed related to substitution of masturbation three times daily, a habit that continues to the present. Much like the self-mutilation of her adolescence, Emily considers the masturbation to be a source of tension release. During masturbation, she often fantasizes about being raped or otherwise forced into sexual activity: it is as if the tormented soothing of cutting had been replaced by the sadomasochistic erotic fantasy.

Case 3

June is a 29-year-old, unemployed African-American woman with a long history of self-cutting. Cutting began at age eight soon after being sexually abused by a friend of her parents. The sexual molestation occurred many times but spontaneously ceased after about a year. June would cut herself immediately after an episode of molestation because she felt she needed to, literally and physically, feel her emotional pain: "Talking about it wasn't intense enough." Cutting lessened in adolescence when she began to act out in school, skipping classes, fighting with classmates, and having indiscriminate sexual encounters with boys. After high school, June eventually became monogamous and stopped self-cutting. About five years later, it started again when a male companion had become physically abusive towards her. After leaving that relationship, the behavior again ceased. However, since then, June finds that affectionate sexual play is not satisfactory to her. During sex, she likes to pretend that she is being beaten or raped, a form of self-abuse that is possibly akin to cutting.

Her parents were intravenous drug abusers who lived together at the time she was born. Soon after, the father contracted HIV and eventually passed it on to the mother. The latter was severely verbally abusive to June. The father has since died. Her relationship with her mother remains ambivalent. To date, whenever mother and daughter argue, June finds that she wants to scratch herself. Blood is not drawn, nor is that her intent.

June's self-cutting relieved tension, as it almost always followed the mother's verbal abuse. It also seemed to be related to an inability to feel satiated emotionally by verbalizing pain. Over time, she replaced cutting herself with acts of physical aggression toward others, sexual promiscuity, and masochistic sexual fantasies.

Case 4

Rebecca is a highly intelligent 22-year-old African-American college student with a record of academic excellence dating back to childhood. She also has a history of self-cutting that began at age twelve and ended at fifteen. She recalls that the impetus for this behavior began with reading a magazine article written about a young woman who had had experiences much like her own and had found emotional release through the act of self-cutting. At a younger age, Rebecca had experienced many events that left her anxious and tense. First, she had been sexually abused by her grandmother as a young child. Next, her parents divorced when she was twelve. After the divorce, her father made no attempt to contact the family again. Rebecca had been closest to her father; he had given much love, attention, and intellectual encouragement.

She found the razor cutting across her skin particularly pleasurable. She also enjoyed watching blood being expressed from the site of the cut. As she discovered such pleasures, she cut herself habitually whenever she was sad, especially if the sadness was accompanied by an urge to cry. Cutting decreased when she began drinking alcohol, but did not stop until age fifteen. Several factors seem responsible for its cessation. She was discovered by family members, who shamed her for her behavior. She also began writing in a journal about her personal experiences and mental pain. Journal writing became an increasing part of her personal life. During these years, whenever she felt the urge to cut, she would go to the bathroom and intently look at the collection of used and bloodied razors; this substituted, she reported, for the literal act of self-cutting.

DISCUSSION

A symptom neither arises nor is resolved independently of other conscious and unconscious aspects of the patient's mind and the relation between the patient and the therapist. With such proviso, we want to assert that all four patients presented here demonstrate the phenomenon of symptom-replacement. Self-cutting is replaced by receiving tattoos (Inez), sadomasochistic sexual fantasies (Emily), fighting and provocative role-playing during sex (June), and wistfully looking at bloodied razors (Rebecca). An explicit form of self-mutilation is thus transformed into its "aim-inhibited" versions (4). Yet important differences in the four cases can be discerned. Inez, the patient with the most traumatic background, replaced self-cutting by another assault on her body, tattooing. Emily and June channeled self-destructive propensities away from body into mental life, binding their masochism with libido to create erotic sadomasochistic fantasies. Rebecca showed a mixed outcome. On the one hand, masochism moved from body to mind

(although unerotically). On the other hand, she began to write about the internal distress that had given rise to self-cutting in the first place, showing ego growth and an adaptation akin to sublimation.

The difference in the outcome of self-cutting in these patients is multiply-determined (5), just the way the symptoms themselves were. Three variables readily come to mind. First is the intensity of childhood trauma. Second is the degree of constitutional resilience, present in one instance in the form of high intelligence. The third is the presence of a reasonably sustained good object relationship during childhood. Among our patients, the one most traumatized could only advance from a naked form of violence against her body to becoming tattooed. On the other end of the spectrum is the patient who had received much love from her father in early childhood and also had high intelligence; she went from cutting to merely looking at razors, also making journal entries about her anguish that, in turn, paved the way to deeper psychotherapy. The outcomes and predisposing factors for the other two patients belong somewhere in between these two extremes.

Such observations suggest that symptom-replacement might be a frequent occurrence during the course of development. If so, a number of factors seem responsible for such an occurrence. With growth, the body changes and so do its psychological meanings. Newer fantasies arise, ego grows, and, in the throes of adolescence, super-ego becomes more abstract and softened (6). Greater life experience provides trials for identifications and realignment of ideals. All this results in changing symptomotology. Depending on the balance of libido versus aggression in the psychic economy, a symptom can become better or worse or be replaced by a parallel symptom.

And symptom-replacement can occur as a result of psychotherapy too, of course, especially in resident-run clinics, where patients derive psychotherapeutic gains largely from ego support, survival of the therapist's containing capacities (7), and inexact interpretations (8). Indeed, the emergence of a milder symptom in place of a more disturbing one might even be a cause of celebration. This has technical significance: when the emergence of a new, but less disturbing, phenomenon can be correlated with the subsiding of a parallel, more severe symptom, the technical approach should not center upon deconstruction-interpretation. Instead, affirmative interventions and provision of ego support for the new compromise formation should be the centerpiece of the therapeutic strategy (9).

Regardless of its context, whether developmental or in psychotherapy, symptom-replacement in regards to self-mutilation appears to be a frequent and often salutary occurrence. Keep in mind, however, the data we present here is limited. As a result, our hypotheses and speculations must be regarded as tentative.

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First-Known Hypnopompic Hallucination Occurring In-Hospital: Case Report

Paul Ballas, D.O. (PGY2)

ABSTRACT

Despite the high prevalence of hypnopompic hallucinations in the community, to our knowledge there are no reports that have been published in the English literature of these phenomenon observed by staff in the hospital setting. Psychiatric or neurological evaluation often ensues if a patient reports hallucinations in other circumstances, but when they are reported in connection with sleep, further evaluation is rarely performed because such events are common in the general populace. Our report emphasizes the distinction between hypnopompic and hypnagogic hallucination as an ongoing feature of life that someone is aware of, which we believe to be the case for normal persons who have them, and a similar hallucination occurring for the first time in someone who is unaware of it, at least unable to remember it. In the latter instance, we suggest careful interview for symptoms of a sleep disorder.

Hypnagogic (prior to sleep onset) and hypnopompic (upon arousal from sleep) hallucinations are both phenomena that occur in normal people and symptoms that are characteristic of narcolepsy (1, 2). They are a common occurrence, experienced by almost everyone at least once and have also been shown to be associated with the use or withdrawal from certain medications, specifically, tricyclic antidepressants, opiates, and donepezil (3-5). Although hypnopompic and hypnagogic hallucinations are generally considered to be normal phenomenon, they have increased incidence in several psychiatric and neurologic disorders (6). One study of over 14,000 subjects revealed that people with anxiety, depression, or bipolar affective disorder have a two-fold increase in experiencing hypnopompic or hypnagogic hallucinations at least once weekly. The same study showed that people with adjustment disorders have a 1.5- fold increase in experiencing these phenomenon at least once weekly (6-8). The notion that such phenomena are normal may be part of the reason behind the wide variation in the literature with regard to their lifetime incidence (hypnopompic 6-13%, hypnagogic 25–38%) (4, 9-11). Over 50 percent of people who experience them have no

appreciable physical disorder, substance-abuse disorder, sleep disorder, or other psychiatric disorder (12).

CASE REPORT

F.R. is a 41-year-old African American woman who had been admitted to the medical service after one day of shortness of breath and two weeks of dull chest pain, night sweats, and a non-purulent productive cough. She had recently completed a 3-week corticosteroid taper and a full course of azithromycin for an upper respiratory infection. The patient had a long history of asthma, hypertension, and gastroesophageal reflux. She also had suffered from Grave's disease in the distant past; hypothyroidism developed later on but has been corrected with thyroxin. The patient was compliant with her outpatient medications: levothyroxine, hydrochloro-thiazide, montelukast, Protonix, fluticasone/salmeterol, continuous home oxygen, multivitamin, and inhaled albuterol. She had no personal or family history of neurologic or psychiatric disorders.

These medications were maintained, and intravenous corticosteroid was initiated. Albuterol was given every 2 hours by nebulizer. Part of the protocol at this hospital for someone receiving nebulizer treatments so often is that physician-reassessment must take place before each treatment. On the first night, after approximately four hours of sleep, the patient was awakened for the second time; she promptly sat up in bed, looked at her right arm, and yelled, "There's blood all over my arm!" The resident physician (one of the authors, P.B.) examined her arm and saw only a clean IV placement. He informed the patient of this, but she looked back at her arm and proffered it again saying "Look, can't you see all this blood?" Again the physician reassured her that there was nothing there, the patient sat still and allowed herself to be evaluated. She showed no signs of a formal thought disorder or of delusion, and she denied any hallucination apart from feeling and seeing blood on her arm. Speech was organized normally. Neurological exam was normal. Respiration remained labored, but after the assessment she went back to sleep.

She was examined several other times over the next day and at no other time during the admission did she have any other hallucinations or exhibit any signs or symptoms of a neurologic or psychiatric disorder. When asked about the incident, the patient had no memory of the hallucinations although she did remember being awakened multiple times. When questioned about her sleep outside the hospital, the patient did not know if she snored or had apneic episodes, but did report poor

sleep quality (frequent unintentional awakenings) and excessive daytime sleepiness. She was referred to a sleep specialist for further evaluation.

DISCUSSION

This case shows that even with no history of prior psychiatric or neurologic disorders, patients in the hospital can have quite striking hallucinations upon awakening. Given the high prevalence of hypnopompic hallucinations among normal persons, it is no surprise many clinicians tend to disregard isolated incidences such as the one described. And yet people who experience unusual sleep-related events typically have been aware of them their entire lives. For example, in adults who experience sleepwalking or sleep talking there is a high prevalence of these phenomena since childhood (13).

We believe it is reasonable to do an in-depth interview specifically for sleep disorders in every patient who experiences a hypnopompic or hypnagogic hallucination for the first time. Sleep disorders are common, debilitating conditions that often go undiagnosed, yet they increase the risk of substance abuse and psychiatric disorders (9, 10, 14, 15). If the interview turns up symptoms consistent with a sleep disorder, often a referral to a sleep specialist will be indicated.

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A Kind of Poem for My Friend and Me

Hilary O'Neill, M.D. (PGY4)

Physicians are taught to use technical, objective, impersonal language. Does a person lose personhood if she's described as "a 54-year-old African-American presenting with increasing lethargy, frequent crying spells, hopelessness, helplessness, plus suicidal ideation"? Or, more condensed even, "a 54 yo AAF w/ hx BAD,1."

Coffee in my M-mug, and grief's palpable. It's my opinion. I don't know about an afterlife. Watching her die made me think of my end, too. Grief is palpable. Nothing's felt right off: so we're taught. I went to work next day. What else is to be done? Stop? I could see myself cold and callous: I'm training myself to be professional. I'm a doctor. My friend's dead, nonexistent. L just called: it's true, M's dead.

Apologies. "Sorry for your loss." Thanks. Shame. Of course I'll miss her. And your excellent care of my friend, thanks so much, Dr Z. Goodbye. A bunch of us read Joyce aloud together in her room. Talked of our love of her company as she went right on dying. We were opposed to it, but not to her wish, for it was her wish. No relatives there; none had been called, none. She trusted us, her friends, our band of eight. We followed her commands. Those things of hers I wanted, like the Chinese tea chest; but I didn't get it: another and better friend put in her claim. How could she? How could she not know what it meant to me. Well… "I never said I want *that*!" I wonder if M might have thought we went for the spoils before she was cold, even. My grandmother used to say, "Would you be in my grave as quick as you're in my chair?" Marking territory, *homo sapiens* finding her way home. I held her hand thinking it might be, just could be, the last breath: she and me.

Can I know how another feels? Feel yourself in another's shoes. Can't happen, of course, if the other isn't feeling. My life progresses, and my attitude about you does, too. Family trees get bigger, leaf out. I mourn all the changes, losing childhood even as I get the college of choice.

I'm lonely a year and a day after M died. I look around for her business card, call the old number. Lo! Her voicemail still works; I say I miss her a lot. Voicemail for the dead. I feel better. Therapy is messaging the dead.

I'm vague about existentialism, feels like nihilism. I used to read Jean-Paul Sartre. Didn't occur to me then there are times for meaning and times for meaningless. It's grey in the tunnel: grey at the end, too, maybe. Not winning wars but living lives. The Oedipal phase, triangulation; Shakespeare and the web we weave; triangles, lines, family trees, missing the forest for the trees. Me, you, me, God, existentialism; I, my aunt, I, my grandmother (which?); mothers, fathers, mine?

Last night I read old journals I'd kept in college, crying, crying: all this way, all this way since then, and I still say the same things to myself. My friends, now in memory, seem more distinct than they were then, on paper. Scary. Still, it's my handwriting; yes, it is. I don't remember now each one I wrote about then. I loved. I got angry. Ill-understood passions. Go on. Apologize later, cut and run, stay; be happy. Combat rock, Clash; is it a jagged little pill? For music soothes the savage beast; others it lulls to dreamland. The universals: music, dancing, celebrating, mourning. The custom of the uncustomary. What sense is there in waking (one is as in "I went to the wake") the dead? I think wakes are sad and celebratory, for the life that's gone and the life going on. I've been to a couple. Not unhappy, not happy. The meaning is not all about being happy, for which there's neither pill nor secret. (Only two sure things, says Poor Richard.) Our Declaration guarantees us the pursuit not the capture of it. Nor is the meaning all sad, although sad has a big role in the thing; maybe there's a pill for that. Not for me, though, given my natural gift already of it. I used to like math, thinking it had a lot of the answers: you got them or not. Then I liked literature: a study of people in their time by someone in it, their time, with them. I love psychiatry; I love medicine; I love the black, white, and grey of them. Points, so many, many points, of view. Right and wrong and happy and sad and lines and triangles and enviously or jealously and Latin and English or Greek and English or English and English and so forth.

Once I wanted to be a veterinarian. My brother sneered, "You want to be a doctor because it's the most prestigious!" I cried and cried. Can't be true. "You don't know anything about me! I want to help dogs and cats and hamsters." Or was it true? I thought then prestigious was a bad word, one I could never know and therefore bad. Makes me laugh now. Not the word being bad but the way he said it. Maybe he was explaining something. Maybe big brothers are not so…

People ask me if 40's really bad. No. Twenty nine was bad, 39, too. I hope I get to know about 49.

Is my green like yours? My blue your blue. Yellow's like sunshine, yellow's the streak on my back. Red is my fury and that flapper's dress, I imagine. ROYGBIV or the rainbow? Is there no word rhyming with orange? I live alone, don't I? With somebody or everyone else?

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Mourning

Salman Akhtar, M.D.

The mere mention of the word "mourning" floods the mind with visions of tears and funerals and sounds of wailing and sobbing. Images of crying men and women, rituals of cremation, or of a body being lowered into a freshly dug grave, and tear-soaked words of condolence are among our immediate associations to the word. That it should be so is understandable, for loss of a loved one by death is the most potent trigger of the emotional reaction called mourning.

Used in a broader fashion, the term "mourning" also refers to the chain of sentiments aroused by any loss, big or small (1). This can range from the loss of physical health to that of material wealth. Surgical amputation of a limb can stir up a mourning reaction just as one's car being stolen can. Less dramatic events also have the potential of mobilizing the emotional sequence associated with mourning. A missed appointment with an out-of-town friend, a misplaced Montblanc pen, and an unexpectedly bad result in a college admissions test are all capable of causing us to mourn.

MANIFESTATIONS AND VARIABLES

Such a broad conceptualization of mourning has commonalities with its narrower usage. In either instance, mourning comprises of a set of emotions that unfold over time when one is faced with a loss (2-4). Shock and *disbelief* ("But I met him just last week and he appeared fine!") are the immediate responses. These are soon replaced by *emotional pain* and a desperate sense of *longing*. Depending upon the gravity of the loss, there might be *physiological disturbances* accompanying this stage. Pacing, sighing, clutching one's chest, pulling at hair, rubbing hands, loss of appetite, and disturbed sleep are often evident. As time passes, the turmoil seems to settle. The lost person is talked about in exalted ways and all his or her blemishes are glossed over; a lost object is an *idealized* object, mused Freud in his seminal paper "Mourning and Melancholia" (5). A mentality of *bargaining* also sets in: "Had I only done this or that, this loss might not have happened". Fleeting

moments of *self-blame* appear, although sustained feelings of guilt are not typical of ordinary grief. More often one encounters irritability and even *anger* at the occurrence of the loss in the first place. Sooner or later, this too passes. A sense of profound *aloneness* and *sadness* now takes over. The bereaved finds himself or herself *fluctuating* between heartache, pining for the departed one, dull indifference, and the dawn of resigned acceptance of the changed life situation. Gradually the rays of *hope* appear on the psychic horizon and the potential space for a substitute begins to open up. The night, it seems, is turning into day.

Lest this description appear too schematic or stylized, let me hasten to add a few caveats. *First,* grief comes in waves. It waxes and wanes. Just when recovery seems at hand, one is hit by a fresh upsurge of sorrow. Grief is hardly a linear process. The phases described here are useful largely for didactic purposes; human experience is always more complex than a catalogue of symptoms. *Second,* no mourning is ever complete and, by implication, no lost object of our affection is ever totally given up. It only is moved to a different place in one's heart. The pain diminishes, to be sure, and emotions do not get readily mobilized. The wound turns into a scar but the story remains.

A *third* caveat pertains to the fact that mourning is a process that takes its own time; it takes, for instance, about two years to recover reasonably from the loss of a truly loved one or from the breakup of a serious romantic relationship. The process, like the healing of a bodily wound, cannot be rushed. However, it can be delayed if certain complicating factors happen to be on the scene. Mourning over death, for instance, is prolonged if the death was unexpected, occurred in violent circumstances, was the result of suicide, and if the death left many unsettled accounts, so to speak, between the deceased and the bereaved. Moreover, the greater the impact upon the day-to-day reality of the bereaved, the harder it is to resolve the grief. The sudden death of a wage-earning head of a household is thus more difficult to mourn than the passing away of an elderly grandmother who was long-suffering from terminal cancer.

Mourning over the death of a child is profoundly difficult, if not utterly unfathomable. Not only is the occurrence contrary to the natural order of things (e.g., grandparents die first, then parents, then children, and so on), it is tantamount to a murder of dreams and hope for the future. Parents are left with the burden of "survivor's guilt" and find grieving to be a life-long nightmare. The pain is greater when the offspring lost happens to be an adolescent. Having brought the child to the threshold of adulthood and then to lose him or her is truly devastating. The fact that parents are often at cross purposes with their teenage children further complicates mourning such a loss.

COMPLICATED GRIEF

When grief does get stuck or complicated, the manifestations of ordinary mourning get prolonged over time. The tendency to become teary, feel that the deceased is not really dead, or both, normally experienced for a few days or weeks, now extends over months and years. The language changes associated with the acceptance of death (e.g., "Uncle Elvin *is* fond of sweets" changing into "Uncle Elvin *was* fond of sweets") get delayed and the dreams typical of early mourning (e.g., seeing the dead person alive, rescuing him or her from a life-threatening situation) continue long past a first few months.

More significantly, new symptoms appear. The most important among these is a peculiar attitude about the physical possessions of the deceased. Under ordinary circumstances, things left behind by someone dead are (unknowingly) divided into three categories: things that are thrown away (e.g., a toothbrush, socks), things that are given away to the poor (e.g., old clothes, shoes), and things that are kept and passed on as family heirlooms (e.g., jewelry, diplomas, private journals, unfinished manuscripts). Moreover, this disbursement is neither too quick nor too delayed; it usually takes a few weeks to a few months. In complicated grief, however, one notices a disregard for time in this context. One either gets rid of the deceased's things immediately (in a magical attempt at denying the significance of what has just happened) or hangs onto them forever, finding oneself haplessly unable to discard these items.

Another development is that things that ought to have been thrown away (e.g., dentures, old underwear, a glass eye, a half empty bottle of cold cream) are kept and, strikingly, held onto in a very strange way. They can neither be used nor thrown away. They cannot even be seen. Looking at them stirs up extremely painful emotions of anxiety, pain, and sadness. These things no longer remain mere physical artifacts; they become what Volkan has called "linking objects," i.e., things that connect the bereaved with the deceased in unspoken and mysterious ways (6).

In light of this, it is not surprising that the deceased's grave becomes a nidus of complex feelings on the part of the bereaved. In normal grief, the feelings one has towards a loved one's grave include tender respect and a peculiar mixture of wistfulness and a sense of reunion. Visits to the grave occur around the anniversary of the death, religiously dictated occasions, and when new members get added to the family via weddings and births (7); over the course of time, the frequency of such visits diminishes. However, when grief has become complicated, the grave acquires greater emotional charge. One either avoids visiting the grave altogether (and even forgetting its location) or becomes "addicted" to it, going there again

and again. A displaced form of this is the phenomenon of “obituary addiction” (6), whereby an individual with unresolved grief feels compelled to check out the obituary section of the newspaper every day. Not finding the name of a loved one who has died long ago provides an unconscious reassurance; it is almost as if that person is still alive.

One thing this description leaves unaddressed is the cause or, to be accurate, the causes, of a grief remaining unresolved. Certainly the depth of attachment one has with the deceased and the external and internal jagged edges left over by his or her departure contribute to the difficulty in mourning. What, however, goes contrary to common sense is that unresolved aggression, if not actual hostility, towards the deceased plays a significant role in "freezing" the process of grief. The dynamics of this are as follows. When there are unspoken hostile and destructive affects and fantasies directed at someone who dies, letting him or her go becomes tantamount to “killing” him or her; this results from the condensation and telescoping of the repressed anger with the reality-dictated necessity of the aggression implicit in moving away from an object.

ASSESSMENT AND TRIAGE

Since, regardless of specialty, every physician comes into contact with situations of grief and mourning, it is important to spell out some essentials of evaluating an individual in such circumstances. First and foremost, upon hearing that someone’s father or mother or brother or sister or son or daughter has died, the physician must not restrict his or her attention to the medical aspects of the occurrence. Questions must be asked about the expected versus sudden nature of the death, the circumstances surrounding it, and the impact that this death has had upon the bereaved’s day-to-day existence. Next, one should inquire about the funeral and explore the degree to which the bereaved participated in it. The fate of the ashes (if the deceased was cremated) or the location of the grave and the emotions that it arouses (if he or she was buried) should also form a focus of gentle but firm inquiry. The same applies to the physical possessions of the deceased. How quick or how delayed was their disposition? What objects are in the bereaved’s possession and what sort of feelings are attached to them? Raising such questions would allow a glimpse into the progress or blockage of mourning processes. As this conversation is taking place, the physician must also make a mental note of the changes in language that occur with a deeper acceptance of someone’s death (see above).

While known to most physicians, one simple fact can hardly be overemphasized: normal grief does not require medical intervention. It is, by definition, a normal

process. The attitude that all human suffering is not illness must be maintained; some pains are integral to life. This does not mean that individuals in this state of normal grief might not end up at a physician's door. When this happens, curiosity should be directed at the lack of social and familial support that has led to "medicalizing" a normal process. Parallel to such investigation, the clinical approach should consist of empathic remarks, imparting of information regarding the nature of normal grief, and a relatively hands-off policy, coupled with reassurance of availability should matters become more difficult. If, however, there is growing evidence that the grief is becoming complicated (prolonged emotional distress, unchanged language, difficulty disposing the deceased's physical possessions, and so on) then active therapeutic interventions do become necessary.

TREATMENT

The foregoing has implications for the sort of help one needs to offer to those with unresolved mourning. Listening to their anguish must, of course, be respectful and empathic; loss, after all, is not a pleasant affair. The therapist, regardless of whether he or she is in the mental-health field or not, should allow ample psychological space for the bereaved to elaborate their story. It is advisable to not meddle too much with sharp, intellectual comments. What the suffering of grief needs most is "witnessing" (8). Listening patiently and making occasional, brief, and affirmative remarks which demonstrate that one understands the pain of the patient is generally sufficient. The therapist may help the patient to talk in greater detail and encourage the bringing in of the deceased's photographs for the therapist and the patient to look at together. This would facilitate the emergence of hitherto repressed memories and release pent up emotions.

Such credulous listening and affirmative stance should, however, not eclipse a certain amount of therapeutic skepticism. In listening to someone with pathological grief, one must keep one's "third ear" open for the verbal and nonverbal cues of a hostile attitude in the patient towards the deceased (9). Such hints and allusions should be gathered silently at first. In other words, the tragic motif of grief must be allowed to run its course before one begins to point out that the patient has actually been somewhat ambivalent about the deceased. It is only with the conscious recognition and acceptance of negative feelings towards the dead person that the patient can fully come to grips with his true psychic reality. This step is necessary for the proper resolution of grief.

A less known technical ingredient of "re-grief therapy" (10, 11) is the use of linking objects described above. The therapist not only encourages the bereaved to talk more and more openly about his or her feelings of loss but also encourages

him or her to bring "linking objects" to the office. Encountering them, touching them, holding them, and reminiscing about them (and, through these, about one's complex feeling toward the lost person) helps thaw the frozen grief. That inanimate objects should help revive and resolve emotional reactions about someone who himself or herself has now become inanimate is an amazing paradox that, in the midst of tears, can bring a smile of gratitude to our faces. Such, as they say, is life!

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Neuroleptic Malignant Syndrome, with Attention to Its Occurrence with Atypical Antipsychotic Medication: A Review

Sarah Guzofski, M.D. (PGY2), Ruben Peralta, M.D.

ABSTRACT

The neuroleptic malignant syndrome (NMS) is an idiopathic, life-threatening reaction to antipsychotic medication. NMS was traditionally attributed to potent dopamine antagonism of typical antipsychotics, but cases of NMS have now been reported for each of the newer antipsychotics. When NMS is caused by a newer, atypical antipsychotic the presentation differs somewhat; fever, rigidity, and, possibly, death may be less frequent. Diagnostic features, predisposing factors, and treatment are discussed, as is the important matter of reinstituting antipsychotic treatment.

Neuroleptic malignant syndrome (NMS) is an idiosyncratic, life-threatening reaction to antipsychotic medication, characterized principally by delirium, fever, autonomic instability, and muscular rigidity (1). Most cases occur within a month of starting the medication, two-thirds within the first week. NMS develops in 0.02-2.44 percent of patients who are prescribed antipsychotics (2-4); NMS may occur even when doses are in the therapeutic range; the risk is somewhat greater with rapid dose escalation and with parenteral administration.

Hyperthermia, delirium, autonomic instability, and extrapyramidal symptoms in a person treated with antipsychotic medications should prompt consideration of NMS. Classically, the extrapyramidal symptoms of NMS manifest as “lead pipe” rigidity of the limbs; other extrapyramidal signs, such as tremor, and cogwheeling, may be present. The muscular rigidity leads to rhabdomyolysis, which can in turn result in renal failure. A wide range of mental status presentations are possible, but patients are most often mute and stuporous. Laboratory findings include leukocytosis (most often 10-20,000, thought to be a stress response) elevated creatine kinase (can reach 100,000), hypocalcemia (from muscle sequestration of calcium), moderate elevations of LDH, AST and ALT, and elevated serum osmolarity from dehydration. An EEG may show generalized slowing, consistent with delirium (5). Symptoms generally develop over 24-72 hours and, in

uncomplicated cases, the mean duration of symptoms is 13-15 days, longer if caused by a depot medication (2). Serious complications are possible, including renal failure, thromboembolism, respiratory failure from chest wall rigidity, aspiration pneumonia, and arrhythmia (5).

DSM IV-TR criteria (6) for diagnosing NMS are in Table 1. A slightly different set of criteria, proposed by Levenson (5), is also commonly employed (Table 2).

Table 1. DSM IV-TR Diagnostic Criteria for NMS

Severe muscle rigidity and elevated temperature associated with the use of neuroleptic medication as well as 2 or more of the following

- Diaphoresis
- Dysphagia
- Tremor
- Incontinence
- Changes in level of consciousness ranging from confusion to coma
- Mutism
- Tachycardia
- Elevated or labile blood pressure
- Leukocytosis
- Laboratory evidence of muscle injury

Table 2. Levenson's criteria for the diagnosis of NMS*

- Major criteria
  - fever
  - rigidity
  - elevated creatine kinase (CK)
- Minor criteria
  - tachycardia
  - abnormal blood pressure
  - altered consciousness
  - diaphoresis
  - leukocytosis

* 3 major criteria, or 2 major and 4 minor criteria, are required for diagnosis

In the differential diagnosis, infectious, metabolic and neurologic conditions should be considered, depending on associated clinical features (Table 3). An interesting debate has centered around the similarities and differences between malignant catatonia and NMS. These two conditions, affecting a similar patient population, can be so similar in their presenting features that some have argued

that they are variants on a spectrum (7). Because NMS, malignant catatonia, and serotonin syndrome are difficult to distinguish on symptomatic presentation alone, medication history, behavioral prodrome, and timeline of symptom-evolution will be critical to making a diagnosis.

Table 3. Differential Diagnosis

Diagnosis	**Suggestive Clinical Features, Indicated Lab Testing**
Infectious: meningitis, encephalitis, bacteremic sepsis	Lumbar puncture. Consider blood and urine cultures depending on overall clinical picture
Metabolic: thyrotoxicosis, pheochromocytoma	Check TSH, urine catacholamines and metanephrines
Neurologic: nonconvulsive status epilepticus, postictal state	EEG
Drug intoxications: MDMA, cocaine, amphetamines	Urine toxicology
Serotonin syndrome	Associated with gastrointestinal signs and symptoms (hyperactive bowel sounds, diarrhea, vomiting), myoclonus, hyperreflexia
Lithium toxicity	Check lithium level. Myoclonus, hyperreflexia, tremor
Central anticholinergic syndrome	Dry, flushed skin, diminished sweating, urinary retention, dilated pupils
Malignant hyperthermia	Exposure to halogenated anesthetics
Malignant or lethal catatonia	Associated with hyperpyrexia, rigidity, akinesia. Review behavior changes over previous weeks. May be preceded by emotional withdrawal, anxiety, agitation, stereotypies, posturing, waxy flexibility, mutism.
Neuroleptic-induced heat stroke	Suggestive history: warm environment, abrupt onset, no extrapyramidal signs, may have absence of diaphoresis if anticholinergic properties interfere with sweating.

Risk Factors

NMS is an idiosyncratic reaction and cannot be predicted, but there are some identified risk factors. Young age, male gender, dehydration, agitation, rapid dose-escalation, and intra-muscular administration increase the risk (5,8). Prior NMS increases the risk for future episodes. There is some evidence for an association between NMS and the following (9,10): concurrent lithium treatment, poorly controlled extrapyramidal symptoms, patients with affective disorders, iron deficiency, poor nutrition, environmental heat load, catatonia, and those drugs that are more potent dopamine-2 (D2) antagonists.

Pathogenesis

The pathogenesis of NMS is unknown. Observation that NMS occurred with D2 blocking agents lead to the hypothesis that D2 blockade in various regions of the brain explained the presentation: D2 action in the reticular activating system could cause changes in level of consciousness; D2 blockade in the nigrostriatal pathway could cause rigidity; D2 blockade in the hypothalamus could account for autonomic instability and impaired heat dissipation, thus hyperpyrexia from the combination of hypothalamic dysfunction and muscle rigidity (9-11). This theory is now challenged since atypical antipsychotics, with their lower D2 potency, are reported to cause NMS.

NMS and Atypical Antipsychotics

There have been reports of NMS attributed to each of the atypical antipsychotics and all of these medications are listed in the NMS Information Services' Registry (9). The rates and presenting symptoms of NMS in typical versus atypical antipsychotics have not been directly compared (12), but some observations are possible from available information. Of the 55 "probable" or "definite" cases of NMS reported to the Neuroleptic Malignant Syndrome Information Service between 1998 and 2002, 31 patients (56%) were on a typical antipsychotic; 24 patients (44%) were on an atypical antipsychotic (13). Cases of NMS have been reported with even the least potent D2 antagonist, clozapine (2,14).

NMS owing to atypical antipsychotics has possibly a different presentation compared with the traditional syndrome: less extreme CK and temperature elevations and less common and milder rigidity (14,15). A 2003 review of 68 reported cases of NMS from atypical antipsychotics found that the mean peak CK was 5958 and the mean maximum temperature was 38.8. Seventy eight percent of patients had extrapyramidal symptoms. Twelve of the 68 required intensive care and 3 patients died (2). This mortality rate is less than that historically reported in NMS (11,16). Perhaps resulting from improved supportive care, mortality in NMS is declining overall: from 76% prior to 1970 to 11% in a 1989 study, (2,11,17).

Treatment

If NMS is suspected, immediately discontinue all antipsychotic medication, as well as other D2 blocking agents. A medical work-up should be initiated (see above): NMS is a diagnosis of exclusion. Supportive care is the mainstay of treatment for NMS and it should occur in a setting in which blood pressure, cardiac rhythm, and pulse-oximetry can be continuously monitored. Autonomic instability may manifest as hypertension, hypotension, tachycardia, or cardiac arrhythmia. Chest wall rigidity can compromise respiration sufficiently to require

intubation; intubation may also be indicated for severe aspiration pneumonia. Urine alkalinization and adequate support with intravenous fluids may prevent renal failure from myoglobinuria (18). Hyperthermia may require a cooling blanket. Because hyperthermia in NMS is not mediated by pyrogens, antipyretic medications are generally not helpful (1). Laryngeal dystonia, dysphagia, respiratory distress, or delirium may preclude oral intake, so intravenous fluid and parenteral nutrition may be needed (1). Prophylactic measures for deep venous thrombosis and frequent repositioning will decrease the likelihood of complications from rigidity and prolonged immobility (5). The medication list should be reviewed: anticholinergic agents or other drugs that interfere with heat dissipation should be discontinued (1).

Medication may hasten response to supportive therapy and decrease mortality (19,20), but controlled clinical trials do not exist, and drug studies that are available have not always shown benefit (21). The two most commonly used pharmacologic interventions are bromocriptine, a central dopamine agonist, and dantrolene, which facilitates skeletal muscle relaxation via calcium release from the sarcoplasmic reticulum (5,9,22). Dantrolene is available in a parenteral form; bromocriptine can only be administered orally. Symptoms of NMS sometimes return if treatment is discontinued before complete clearance of the offending medication, so, if bromocriptine, dantrolene, or both are utilized, treatment should be continued for ten days beyond the resolution of symptoms, or for 2-3 weeks if the offending agent has been an extended release depot antipsychotic (5).

Oral or intravenous benzodiazepine, the mainstay of early treatment of catatonia, may decrease fever and rigidity in NMS, in addition to treating agitation (1). Respiratory status should be monitored. Positive results have been reported with diazepam (23) and lorazepam (24).

Electroconvulsive therapy (ECT) is another treatment option and may decrease hyperpyrexia, diaphoresis, and delirium, possibly by modulating dopamine activity in the brain. Onset of response, on average, is after 4 treatments (12). ECT should be considered especially for patients who have not improved after 48 hours of pharmacologic treatment, if it is not clear whether the cause of the symptoms is neuroleptic malignant syndrome or malignant catatonia, and if the underlying psychiatric diagnosis is a mood disorder (12,25-28).

Antipsychotic treatment after NMS

Patients with a history of NMS are likely to require future antipsychotic treatment. The estimated risk of developing NMS again with repeat exposure to a D2 blocker is 30%, and the risk of mortality from subsequent NMS episodes is estimated to be as high as 20%) (13). Treatment decisions are further complicated

by the observation that not all patients will experience a recurrence, even if they are treated with the same drug.

There are very few formal studies documenting the outcome of antipsychotic treatment after NMS. Several reviews of this topic were written in the late 1980s (28-30, 32). For example, Olmstead reviewed 29 rechallenges reported in the literature; 13 of the 29 had a recurrence, and 2 of those patients died; the most common agent used for rechallenge was the low potency agent thioridazine (13 of 29 patients, causing 2 recurrences of NMS, one culminating in death) (29). Rechallenges that produce recurrence of NMS are reported with a variety of medications. Rechallenge at least 2 weeks after the initial episode appears to be safer, and recurrence is more likely if high potency medication or high doses are used (1). In a 1989 review, Rosebush and colleagues report that 13 of 15 patients with prior NMS experienced no recurrence on rechallenge (30). And two small, longer-term reviews found that in a majority of patients who are rechallenged with antipsychotic medication NMS does not recur (31,32).

Based on these reviews, on the observed risk factors for NMS, and on theoretical speculation about pathogenesis, we come to the following as recommendations for reinstituting treatment after the first episode, with the understanding that the evidence supporting them is limited. Weigh risks, benefits, and alternatives to antipsychotic medication. If alternatives are poor and the benefit outweighs the risk, restart antipsychotic after a 4-week waiting period following the resolution of the episode. Begin with a low dose, advance slowly toward the target dose, and choose an agent with low D2-nigrostriatal affinity (an atypical or a low potency typical). Monitor carefully for fever, autonomic instability, mental status change, extrapyramidal symptoms, and dehydration. Serial measurements of white blood cell count and CK are warranted. Agitation should be treated aggressively with benzodiazepine, since agitation increases the risk for NMS. Adjunctive treatment with a mood stabilizer, antidepressant, or both for affective symptoms may minimize, possibly, the required dose of antipsychotic (22,29,33). Velamoor has suggested considering prophylaxis with amantadine or bromocriptine (22).

SOURCE INFORMATION

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Editorial: NMS, and Why We Should Call It (Malignant) Catatonia

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The review in the current issue by Guzofski and Peralta, "Neuroleptic Malignant Syndrome, with Attention to Its Occurrence with Atypical Antipsychotic Medication: A Review," reminds me of the influence of a name. I am thinking here of the name, "neuroleptic malignant syndrome" (NMS), which was coined by Delay in 1960, following reports of "catatonic-like" states resulting from phenothiazines, and popularized through an influential review by Caroff in 1980 (1, 2).

A very similar syndrome, recognized as an advanced (excited, lethal, malignant, pernicious) form of catatonia had been described well before the advent of the typical antipsychotic medications. And catatonic features often are an overt feature of NMS (3-5). In addition, simple catatonia is recognized as a risk factor for NMS if typical neuroleptic is given (5). Even so, the name of NMS took on a life of its own, a meme, we might say, that began to spread from one psychiatrist's mind to another independently of the meme(s) for catatonia, despite the efforts of some to stem the tide (3). I offer as proof of this last sentence two first-hand observations. First, I find that few of my peers are aware of a link between, or similarity of, NMS and malignant catatonia (MC). Second, Doctors Guzofski and Peralta did not include much mention of MC in their original submission. And, I suspect, nothing unusual at all resides in either of these observations. A very large number of psychiatrists and psychiatry residents do not realize NMS and MC are linked concepts, that's my guess. I have been luckier myself. Two of my mentors when I was a PGY2 on the Consultation-Liaison rotation here at Jefferson, Dr. David Lynn and Dr. Dimitri Markov, taught me about MC and encouraged me to dig into its literature; as I did that, I learned about its link with NMC. And for that I have most to thank Dr. Max Fink and his colleague, Dr. Michael Alan Taylor (6, 7). They are not the only, or even the first, authors to speak of a link between MC and NMS (3), but Dr. Fink, especially, has been the most declamatory on the topic, the one most emphatic that the matter of language, the matter of the name, has a lot to do with how we clinicians behave.

His point of view is that NMS is a variant of, or a subtype of, MC: MC that happens to have been triggered by an antipsychotic medication. (The same is true,

he believes, of serotonin syndrome: a subtype of MC, one that has been triggered by serotonergic excess.) And this view has a highly practical implication, namely, that treatment that is effective for catatonia should not be withheld from those suffering from NMS. He is thinking of benzodiazepine (lorazepam is used most often) and, should that medication prove ineffective within a few days, electroconvulsive therapy (ECT). The dose of lorazepam that is required is often quite high, so the schedule by which it is advanced will need to be aggressive (taking care not to produce oversedation or respiratory compromise, of course); it can be given parenterally, and should be in some instances (8).

So, having brought the memes of MC and NMS together in your mind, you become vigorous in the application of benzodiazepine. But it is in the early use ("early" in a relative sense) of ECT that your thinking is most changed by comparison with your thinking had the two memes remained estranged. And that's because the NMS meme, as an isolated thing, does not lead to thinking of ECT (or benzodiazepine) early on. It is modeled on another meme (by "meme"—maybe I should be speaking of a whole family of them—I mean, of course, a word or phrase or idea that appears to spread from mind to mind in the Dawkins sense, as a selfish gene might, were it possible for a gene to spread from mind to mind), that of malignant hyperthermia (MH), which brings forward first the idea of supportive care, especially with regard to control of body temperature and fluid volume, and this, of course, is a fine outcome even were MC and NMS two separate things. And next among the weapons summoned up by the NMS meme(s) is the drug dantrolene (a direct-acting muscle-relaxant that affects calcium flux from the endoplasmic reticulum), also bromocriptine (a dopamine agonist to fix the hypodopominergic state that the neuroleptic caused), amantadine (another dopaminergic drug), or both. And uncontrolled but careful clinical studies provide good support for the use of dantrolene and dopaminergic drugs in NMS (1, 5). It's not that their use is to be avoided, it's that ECT should not be put off long if they, as adjuncts to benzodiazepine, have not relieved the disorder within a few days. And Dr. Fink's point is this: ECT *is* likely to be put off too long if the concepts of NMS and MC are not linked in the clinician's mind, brought together in the one idea that the former is a special subtype of the latter. Two excellent books on catatonia, both published recently, support this opinion and document its history (9, 10).

No randomized studies of ECT in MC or NMS exist, but clinical experience with its good effectiveness in these conditions, which I, following Fink and several others, shall link together as one, is fairly extensive (1, 2, 5, 6, 11-14). It appears to be safe generally, but at least two patients have died as a consequence, so some caveats are in order. First is that neuroleptic must be stopped as far in advance of

the procedure as possible (which should have been the case at the time of diagnosis anyway), as the two deaths mentioned were both in patients in whom neuroleptic had been continued (15). The neuroleptic in these cases was a typical one, but the caveat almost surely should extend to the newer, atypical antipsychotics also. Second is that succinylcholine should be avoided as the paralyzing agent for ECT if at all possible; this agent is known to predispose to abrupt hyperkalemia (possibly the mechanism of death for the two cases mentioned), and conditions favoring hyperkalemia are already extant in the situation (muscular injury from rigidity and high body temperature; possible renal compromise from myoglobin-uria and extracellular volume depletion; possibly a direct potassium-releasing effect of ECT on skeletal muscle). The third follows from what has just been said: serum potassium should be monitored very closely and great care should be taken to ensure that extracellular volume has been repleted by adequate intravenous supple-mentation (16).

Thinking of MC, NMS, and serotonin syndrome (SS) as variations on the same theme, that of catatonia, makes it easier for me to remember how they present, mainly as the same picture with some interesting differences: the excited, prodromal phase may be missing and muscular rigidity earlier in NMS; gastrointestinal distress, and maybe myoclonic seizures, more prominent in SS. Seeing the one family makes it easier to pick up the distinctions among its members. And, speaking of families, what a large number of conditions has been reported to cause catatonia! Most of the reports are of the "benign" (simple, retarded) form (BC), but I see no reason to presume that a condition capable of causing BC could not also cause MC, as the latter may occur as an "advanced" stage, or complication, of the former. I have gathered the conditions that I have come across in the literature into two tables. The citations for these, in many instances, are in the articles or books cited in the References section.

Table 1. Psychiatric Predispositions to Catatonia

- mood disorders
  mania or depression: ~ 50% of catatonias; 25-50% of all catatonics are manic
- schizophrenia & other psychoses
  ~ 15% of catatonic adults; higher % in children
- autism spectrum disorders
- obsessive-compulsive disorder (at least the PANDAS form)
- dissociative disorders/hypnosis
- narcolepsy
- periodic catatonia (a rare familial form, maybe autosomal dominant)

Table 2. Medical Predispositions to Catatonia

(Approximately 25% of catatonias have no psychiatric cause)

Neurological

- Von Economo's encephalitis
- HIV
- Chagas disease (acute)
- Lyme disease
- Herpes simplex
- GPI (CNS syphilis)
- subacute sclerosing panencephalitis
- acute disseminated encephalomyelitis
- seizure disorder (esp in children), incl postictal
- postmalarial syndrome, w/ psychosis
- head injury, including subdural hematoma
- subarachnoid hemorrhage
- basilar artery thrombosis
- stroke (often cardioembolic)
- Sheehan's syndrome
- paraneoplastic encephalopathy
- periventricular diffuse pinealoma
- tumor of septum pellucidum
- subthalamic tumor, w/ hydrocephalus
- alcoholic/Wernicke encephalopathy
- multiple sclerosis
- Parkinson's disease
- progressive supranuclear palsy
- dementia with Lewy bodies
- familial cerebellar-pontine atrophy
- hereditary spinocerebellar degeneration
- tuberous sclerosis
- Creutzfeldt-Jacob disease
- bilateral globus pallidus lesions
- frontal, parietal, or thalamic lesions
- arachnoid cyst

Systemic

- SLE
- FUO
- TTP
- Wilson's disease
- liver transplantation
- hepatic encephalopathy
- uremia
- diabetic ketoacidosis
- membranous GN
- hyponatremia
- burns
- staphylococcal infection
- tetanus
- tuberculosis
- infectious mononucleosis
- typhoid fever
- PANDAS
- vitamin B_{12} deficiency
- hyperparathyroidism/hypoparathyroidism
- pheochromocytoma
- thyrotoxicosis
- acute intermittent porphyria
- Addison's disease/Cushing's disease
- MEN, 1
- hereditary coproporphyria
- carcinoid tumor
- homocystinuria
- pellagra
- Tay-Sach disease (adult form)

Toxic Effect of a Medication or Substance

- azithromycin
- ciprofloxacin
- bupropion
- venlafaxine
- clomipramine
- methylphenidate
- lithium
- levetiracetam
- neuroleptic (NMS)
- serotonergic (SS)
- corticosteroid, ACTH
- fluorides
- baclofen
- disulfiram
- cyclosporine
- reserpine
- metoclopramide
- psilocybin
- PCP
- MDMA (ecstasy)
- opiates
- mescaline
- illuminating gas
- alcohol
- aspirin (overdose)
- strychnine

Withdrawal from a Medication

- lorazepam, other benzodiazepine
- mixed sedative
- carbamazapine
- dopaminergic drugs
- anticholinergic drugs
- gabapentin

Hard to shake off vertigo from simply looking at these tables. Harder still to imagine the disorder in the clinician's mind, were there no unifying idea like "catatonia" to bring them together under the one roof: otherwise we would be trying to memorize, I suppose, the neuropsychiatric features one by one that each was reputed to have caused. And we would have no idea at all how to proceed with therapy. As it is, we can know this: *the catatonic illness that each and every one of these disorders can, on occasion, produce is treated in exactly the same way, varying only according to its response to initial therapy, namely, to lorazepam!* Of course, with the exception of withholding typical neuroleptic in all catatonias until the state is relieved, and withholding any antipsychotic, typical or atypical, in the MC variant, it doesn't hurt to treat the specific predisposition to the catatonic state, too, whenever that is possible. Such is the value of a name, the right name. Which doesn't mean the future could not bring a better one, or reveal that we'd be better off with more than one, and which names those should be.

Just why the two names, NMS and MC, fell apart and propagated separately is unclear, to me anyway. It seems that some of the important writers about them in decades past, Caroff and colleagues, and Fricchione and colleagues, took distinct care to see that separate propagation did not occur. And yet it did. (Which is why Dr. Fink has had to come to the rescue.) Perhaps psychiatry contains such variety it has trouble keeping its language from splitting into dialects that soon fracture its citizenry. Perhaps our textbook editors have under-appreciated the phenomenon of catatonia (the topic surely gets short shrift in some), owing to having succumbed to addictive properties in the format of the DSM-IV. The latter has an unstable placement for catatonia (6), apparently out of loyalty, conscious or not, to the outmoded conception that catatonia is mainly a schizophrenic condition. Perhaps NMS, flirtatious as it is with the MH meme(s), has biological cachet for those who are made anxious by the very subject of psychiatry, which is the mind.

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