Hyperventilation-Induced Non-epileptic Seizures in an Adolescent Boy with Pediatric Medical Traumatic Stress

[I] CASE HISTORY

Non-epileptic seizures are common in children and adolescents.[1] M is a 14-year-old boy presenting with non-epileptic seizures and other functional neurological symptoms in the context of pediatric medical traumatic stress and a complex neurosurgical history. M lives with his mother and 11-year-old brother in government housing in a working-class suburb of a major city. His parents separated when he was six years of age, and he visits his father on a weekly basis. M was born with chromosome 8q21.11 microdeletion syndrome;[2,3] he has a slightly dysmorphic face, an IQ in the low average range, and attention-deficit/hyperactivity disorder (ADHD), treated with long-acting methylphenidate 30 mg a day.[2] His cognitive difficulties include a slow processing speed (percentile rank of 2) and difficulties in short-term memory, abstract thinking, and forward-planning capabilities. Functionally, M becomes easily frustrated or angry, and gives up in the middle of tasks that he finds challenging. M has a past history of nocturnal enuresis, is farsighted, and wears glasses. In terms of family history, M's brother and father suffer from ADHD, and his father has a history of learning disabilities as well as anxiety, depression, and alcohol abuse (with recurrent admissions to drug and alcohol rehabilitation clinics). His maternal grandfather suffered from bipolar disorder, and his paternal grandfather suffered from anxiety and migraines.

M attends mainstream schooling, where, in the past, he had been the victim of chronic bullying. In addition, at the age of 12, he was exposed to sexual abuse at a school camp where a large number of boys were molested. The exact details of what happened to M himself remain unclear. M's private psychologist trialed Eye Movement Desensitization and

Reprocessing—with limited benefit—in an effort to process distressing memories of the sexual abuse.

When M was 13 years and 3 months of age, he suffered a spontaneous subarachnoid bleed into the third and fourth ventricles following a one-day history of severe headache and vomiting. On admission M was confused and had a decreased level of consciousness, with a Glasgow Coma Scale of 3/15. Investigations—magnetic resonance imaging and magnetic resonance angiogram of the brain and spinal cord—failed to identify any underlying vascular lesion. In the hospital M was intubated and operated on for an urgent external ventricular drain. Following the operation his intracranial pressure remained elevated due to a noncommunicating hydrocephalus. M was treated in the intensive care unit for a week, prior to being transferred to the ward. The inability of doctors to identify the underlying cause for the intracranial bleed made M very frightened, and he remained fearful that a brain bleed could reoccur and that he would die.

Three months later, aged 13 years and 6 months, M re-presented with severe headache, vomiting, confusion, and a Glasgow Coma Scale of 13/15 secondary to a second bleed in the fourth ventricle. A computed tomography scan of the brain revealed a communicating hydrocephalus and small clot in the dependent posterior horn of the left lateral ventricle. M underwent an emergency third ventriculostomy to relieve the block. Again, cerebral angiography failed to identify any specific cause for the bleeding. M was very frightened by the new bleed, and his worries about death were reignited. Following discharge one week later, M continued to complain of mild intermittent headaches, though they did not require medical attention.

Eight months later, aged 14 years and 4 months, M re-presented to the emergency department with worsening headaches in the fronto-occipital region. This time, MRI scans showed partial obstruction of the third ventriculostomy with associated hydrocephalus.

Because the hydrocephalus persisted, M underwent his third neurosurgery, where a ventriculo-peritoneal shunt was inserted to drain his cerebrospinal fluid. The surgery was complicated by facial swelling and a CSF leak.

Following the third surgery M had multiple presentations with headache to the emergency department—11 presentations in eight months. Over time the presentations became more complex and, in addition to headache, his symptoms included abdominal cramping, blurred vision, occipital pain, and visual and auditory hallucinations. Investigations—blood screens, extensive X-ray series (looking at the shunt), serial brain-imaging studies, and electroencephalograms (EEG)—failed to identify an organic cause for the recurring headaches. M was referred to Psychological Medicine for assessment of hallucinations because his neurosurgeon and neurologist were concerned that he might be developing a psychosis.

[2] First Outpatient Evaluation

M attended the Psychological Medicine appointment with his mother, Mrs. W, and his younger brother. The assessment involved the team child psychiatrist, a clinical psychologist, the clinical nurse-consultant, and the team's psychiatric resident. The process of telling the medical story—during which, M became very aroused and described his memories in vivid detail—suggested that M had been traumatized during his hospital admissions. His increased arousal was marked by hyperventilation (counted at 32 bpm, with a normative baseline rate being <20 bpm). Mrs. W reported that M ruminated about the admissions constantly and looked continually at the "selfies" he had taken on the hospital bed, when hooked up to various tubes and monitors; eventually, Mrs. W felt forced to lock the pictures away. M

agreed that he could not stop thinking, night and day, about his hospital admissions, and said that he was plagued by vivid images of being resuscitated.

When asked about his headaches, M reported that the onset of a headache precipitated his fear of dying, made him anxious that his shunt would block again, and reactivated the images of his hospital admissions. M was able to differentiate two different patterns of headache: the first type was "horrendous" and associated with increased ventricular pressure, and the second was less intense, occurred every two weeks, fluctuated in intensity, and occurred mostly at school, when M was challenged with school work.

When asked about his auditory hallucinations, M reported that he had begun to hear voices prior to his last neurosurgery, four months earlier. The voices occurred mainly at night when M was tired, and they irritated him because he could not understand what they were saying. At the time of the assessment, the voices had largely resolved. Another type of auditory hallucination pertained to an imaginary friend called Frank, with whom M chatted. Frank had been a long-term source of comfort, and he tended to emerge whenever M was stressed.

During the assessment interview, M was able to tell a coherent story about his experiences, but he often jumped from one idea to another, consistent with his ADHD, which was only partially responsive to the long-acting methylphenidate. Toward the end of the interview, a physical examination confirmed ongoing hyperventilation along with significant pain and tension in his neck, shoulder, and trapezius muscles, suggesting a chronic state of stress.

The interview ended with a formulation regarding M's symptoms. The team hypothesized that M's hallucinatory experiences represented a symptom of stress rather than a primary psychotic disorder. Likewise, the lower-intensity headaches were conceptualized as a symptom of stress. M had trouble understanding the formulation, but Mrs. W immediately

understood that M had found the hospital admissions traumatic and that his somatic symptoms emerged in the context of significant arousal and distress. It was agreed that M would continue to see his psychologist for ongoing anxiety management and for processing of traumatic material.

[2] Second Outpatient Evaluation

M's symptoms decreased in frequency and intensity during the school holidays. As the beginning of the new school year approached, he began to present to the emergency department with new symptoms, including disturbed sleep, ataxia and blurry vision, fainting episodes and seizures. After extensive investigations—multiple imaging studies, X-ray series looking at M's shunt, and EEG—M's neurosurgeon and neurologist concluded that the symptoms were functional. The second evaluation with the Psychological Medicine team, over two sessions, took place when M was 14 years and 11 months of age.

During the Psychological Medicine assessment, M experienced a non-epileptic seizure, and the team was able to track the temporal order of events. M's anxiety was triggered by a conversation about his new symptoms. He became visibly distressed, began to hyperventilate at 40+ bpm and was unable to slow his breathing. He eventually slid from his chair to the ground and shook violently for five or more minutes.[4] M was put on a waiting list for an inpatient admission to the Mind-Body Rehabilitation Program, a program for children and adolescents with functionally impairing somatic symptoms.[5,6] In the meantime, he was started on a trial of fluoxetine—with the aim of decreasing his arousal and subjective anxiety.[7]

While awaiting a place in the program, M attended weekly individual sessions with the team psychologist, but he was unable to implement any interventions, including breath-training exercises that used biofeedback.[8] M would typically want to talk about his medical

experiences, a process that appeared to perpetuate his anxiety, fear, and increased arousal. M also continued to present to the emergency department with functional neurological symptoms.

M's situation was further complicated by the community psychologist's failure to return calls and her impression, according to M's mother, that M suffered from epilepsy. In this context the school had received mixed messages about M's seizure-like events. The neurology/neurosurgical team had communicated that his events were stress related, but the psychologist insisted that M had epilepsy. Not surprisingly, the school staff were confused and at a loss at how to manage M's events. M was also confused about his diagnosis.

[2] Inpatient Intervention

[3] Hyperventilation challenge: confirming the diagnosis

M was admitted to the Mind-Body Rehabilitation Program, which was run from the adolescent medicine ward, for management of non-epileptic seizures. In the hyperventilation challenge test, the EEG showed that M's pCO2 level was compromised at baseline: 30 mm Hg, compared to the homeostatic range of 36–45 mm Hg. This result was consistent with the team's clinical observations that M was in a state of chronic hyperventilation. With five minutes of hyperventilation, M's pCO2 dropped to 16mm Hg, at which point he felt dizzy and started jerking. During the 15-minute recovery period, M's pCO2 did not return to homeostasis. The test confirmed the team's clinical observations regarding M's non-epileptic events, and it enabled M to "buy" the team's formulation that his fainting and non-epileptic events were stress related. M was fascinated by the diagram showing the drop in pCO2 levels during hyperventilation (see Figure 1). He was able to understand that hyperventilation

lowered his blood level of carbon dioxide, that this drop caused his brain arteries to spasm, and that this response caused him to faint or experience a non-epileptic seizure.[9,10] The treatment was for him to gain control of his breathing and for the team to do some mind-body work with M to decrease his distress and enable him to control his body better.

[Figure 1 about here]

[3] Using the admission to process medical traumatic stress

The adolescent ward is run as a therapeutic environment; admission involves attendance at school, a daily adolescent group, and parents visiting the adolescent but not staying in the hospital overnight. A key aim of the Psychological Medicine team and the ward nursing staff is to form good relationships with the adolescents who stay on the ward so as to make the hospital stay a positive experience. Because M had been traumatized by his past admissions, the team was hoping that admission to a therapeutic ward would function as a positive experience and thus as a form of desensitization to the traumatic nature of hospital. The team used the daily ward round as an opportunity to connect with M. Despite his initial reservations about being treated by the Psychological Medicine team, he quickly engaged with all team members, became fond of his treating team, and looked forward to both the ward round and his therapy sessions. M's shift in perception was reflected in the way that he addressed the team; his original term, "the psycho team," changed to "my medical team."

Certain aspects of the admission elicited trauma-related material. For example, during the first half of the admission, M was worried that a pedophile could be lurking outside the ward and looking into his window, and he became unsettled by an abstract painting on the wall. Toward the second half of the admission, however, these fears receded into the

background, and M reported that the window and the painting no longer bothered him. As M formed relationships with the nursing staff and the team, he began to talk about the past sexual abuse. When the abuse came up, the team encouraged M to be more open with his mother so that she could also support him.

[3] Pharmacological Intervention

Early into the admission it was noted that M had an elevated mood, that he was hyper-verbal, and his thinking processes were even more tangential than normal, with M shifting unpredictably from topic to topic. The fluoxetine, was thought to be the likely cause of this hypomanic state and was ceased. M's mental state began to settle.

From daily nursing observations, it was noted that M had an elevated resting heart rate that ranged from 80 to 120 bpm—corresponding to the 75th to 99th percentile.[11] This elevated heart rate, which was flagged as abnormal on the hospital's standard pediatric observation chart system, was most likely secondary to his prescribed methylphenidate (30 mg per day),[12] A trial off the methylphenidate resulted in a decreased heart rate, but the hospital school, his therapist, and his mother reported that M's concentration issues were unmanageable with the stimulant medication. A compromise of 20 mg methylphenidate per day was agreed upon.

Clonidine 25 micrograms was added at night to address M's long-term sleep disturbance and to decrease arousal (clonidine, an α2 agonist that acts on the amygdala, can be helpful in down-regulating arousal in children who have been traumatized).[13]

[3] Structuring the individual psychological treatment sessions

Now that M understood the physiology of his non-epileptic events, he was motivated to work hard in his individual therapy sessions. The sessions were highly structured. M was not allowed to talk in the first 20 minutes. Instead, he had to use that time to practice his diaphragmatic breathing. He did so by lying down on a yoga mat with a plastic cup on his abdomen, with the expectation that the cup would move up and down if he was doing the breathing correctly. M required frequent redirections to stay on task. The therapist experimented with different sensory modalities and found that when M felt out of control and flighty, he liked a weighted neck bag or weighted leg bags to help ground him.[14] M found it especially useful to practice his breathing with the weighted bags grounding him in his seat or on the floor while he counted his breaths to help him focus.

Within a two-week period, M was able to decrease his breathing rate to 20 bpm and to implement the breathing on his own (i.e., without supervision). With subsequent practice, many months later, he improved even more, decreasing his breathing rate to 9 bpm.

M was also able to utilize a body map to help him identify when his body was becoming aroused; relevant signs included faster breathing, mild headache, blurry vision, dizziness, nausea, wobbly legs, sweatiness, tightness in his throat, neck locking with a high pitched voice, and becoming emotional (upset or angry). In the "tool box" that he developed with his therapist, he placed cards with different strategies: slow breathing; the use of sensory-grounding strategies (a weighted lap bag and a weighted neck bag, which M used in school to help him feel grounded); a mindfulness intervention (tracking his body sensations in a neutral curious manner) that helped him let go of the body stress; a mindfulness intervention (taking note of his thoughts and letting them go) that helped him let go of other people's problems; and asking teachers to help younger distressed children rather than trying to solve their problems himself. M also developed a small cheat sheet with his therapist that

visually depicted the therapeutic interventions he could use and which he could carry around in his pocket. For example, M used the image of a frog to represent slow diaphragmatic breathing, and an anchor to signify his grounding interventions.

[3] Practicing the breath intervention in the ward and school settings

The breath training was then extended to the ward and school settings. On the ward, M was supervised to use it to both prevent and manage his non-epileptic events. Staff found that they had to be firm with M—for example, by prompting him in a clear and direct manner, "do your breathing." The same management plan was subsequently implemented at M's home school. As a preventive strategy, M practiced his breathing three times, under supervision, during the school day. Episodes were managed quietly, with one staff member instructing M to "breathe slowly" if he became distracted by fearful thoughts. Spectators were banned.

Because M liked visual aids, the school purchased a heart-monitor watch. M was expected to implement his breathing or other de-arousal strategies during class if his heart rate increased over 100 bpm. M's mother, Mrs. W, was likewise taught to supervise the breathing intervention so that she could help M implement it at home.

[2] Outcome Post Admission

M did extremely well post-discharge. The one significant non-epileptic event in two months was well managed by M and the school according to the plan that had been put in place. The psychologist from the Psychological Medicine team continued to call Mrs. W and M's school on a weekly basis to provide support over a period of 2–3 months. M continued to utilize his toolbox. There were no further presentations with functional somatic symptoms to the emergency department. Because sleep continued to be a problem, melatonin was added to

M's medication regimen—20 mg methylphenidate and 25 micrograms clonidine—which his pediatrician managed on an ongoing basis. M also continued to work with his private psychologist to process traumatic material.

[2] Relapse 15 Months Later

15 months post-discharge, M re-presented to the Psychological Medicine team with increased distress, deterioration in school functioning, pressured speech, and tangential thought processes, along with a relapse of fainting episodes. The triggers identified at this time were his father's deteriorating mental health (which resulted in hospitalization) and the increased stress connected with a more demanding school year (10th grade). M had also gained a lot of weight; body mass index (30.67 kg/m2) was now in the obesity range. In addition, M and his mother reported that M had been skipping school, that he had significant anxiety about completing schoolwork, and had gotten into a fight at school, which had resulted in his suspension. M's school confirmed these reports.

[2] Admission to Hospital for a Medication Change

M's deteriorating functioning prompted rehospitalization to reevaluate his medication regime. The admission to hospital confirmed that M suffered from an elevated mood. In addition to the symptoms already described, it was noted that, in hospital, M was making inappropriate sexual comments to some of the other patients.

Over a two-week period, M was started on aripiprazole (increased to 5 mg). olanzapine (2.5 mg) was used temporarily at night during the admission to control of M's insomnia. The methylphenidate was withdrawn over a two-week period; it was still contributing to M's arousal (as evidenced by increased heart rate), and the slow withdrawal minimized the possibility of agitation secondary to the commencement of aripiprazole.

Aripiprazole was chosen because of its mood-stabilizing properties and because it was likely to be of some help with regard to M's attention problems.[15] It was also unlikely to result in weight gain, which was now a significant issue in M's management.[15] A full endocrine workup was conducted to exclude any potential organic contributors to M's increased appetite, and he was also referred to the obesity clinic. During the admission, M engaged in the mind-body program that he had previously attended, which included hospital school attendance, individual therapy sessions to top up his skills in slow breathing and anxiety management, adolescent group therapy, and daily physiotherapy to develop an exercise program.

[2] Outcome Following the Admission

Following a two-week admission, M was discharged on 5 mg aripiprazole, 50 micrograms clonidine, and 3 mg melatonin. Follow-up involved weekly telephone contact with the team's resident, monthly outpatient appointments with the team's psychiatrist, and regular sessions with his private psychologist. M settled over a three-month period. His school reported significant improvement in functioning. The changeover to the life-skills program resulted in full-time attendance at school. The fainting episodes ceased; sleep improved; and the disinhibited behaviors settled. Despite these positive changes, M continued to experience significant anxiety regarding his performance at school and also about his career prospects for the future. A life-skills program was organized as part of his schooling. The team reminded M, his mother, and his school that he possessed the tools needed to manage his anxiety and that his therapy sessions with his psychologist should be used to integrate those tools into his daily life.

[1] QUESTIONS TO THE CONSULTANTS

- What are the predisposing, precipitating, and perpetuating factors for psychogenic non-epileptic seizures (PNES) in this case presentation?
- What are the mechanisms underlying this patient's PNES, and how can these mechanisms be targeted for treatment?
- What is the association between PNES and panic attacks?
- How are PNES to be understood neurobiologically?

[2] Consultant 1

This complex, compelling case highlights many of the challenges observed in the diagnosis and management of psychogenic non-epileptic seizures (PNES) and their accompanying symptoms. M's history showcases many of the predisposing, precipitating, and perpetuating factors usually encountered in patients with PNES and other functional neurological syndromes.[16] His baseline intellectual limitations, chronic bullying, and past history of sexual trauma are some of the predisposing factors that position M at a vulnerable state, compared to his peers, in terms of his ability to cope with stressful life situations, including medical stressors. Individuals with learning and intellectual disabilities represent a specific subpopulation in PNES, with one study of 288 patients showing an 8.6% prevalence of learning disabilities.[17] Patients with PNES who are intellectually disabled are more prone to have identifiable situational triggers for their episodes and also report lower rates of sexual abuse when compared against those without learning disabilities.[18] In M's case, the recurrent medical traumatic experiences served as precipitants for the eventual development of several somatic expressions of distress, one of which was PNES. Perpetuating factors include the uncertainty regarding his medical condition and also family and school responses, which probably inadvertently reinforced symptoms.

More than two- thirds of adults with PNES identify past traumatic experiences[17]; in pediatric PNES, more than 90% of patients report a history of lifetime adversities.[19] While

sexual abuse and physical abuse are the most common traumatic experiences reported by adult PNES patients,[17] medically related trauma, psychological abuse such as bullying, and domestic and community violence are the most commonly reported adverse life events by child and adolescent patients with PNES.[19] We consider M as suffering from recurrent traumatic experiences of multiple types that led to a chronic state of hyperarousal signaled by his chronic hyperventilation and somatic hypervigilance, among other more classical symptoms of posttraumatic stress disorder (PTSD). Attention and other cognitive difficulties can also be explained in the context of a chronic hyperarousal state, as can his transient auditory hallucinations.

A baseline level of autonomic hypervigilance has been documented in PNES subjects.[20] In a previous publication, it was hypothesized that during PNES, patients alternate between, and can even simultaneously present with, symptoms of hypo- and hyper-arousal.[21] The hypo-arousal response manifests with a disengaged cognitive process (as described in dissociative states) and with emotional distancing (such as during M's fainting episodes). The hyper-arousal response manifests itself with hypervigilance, excessive emotional and autonomic reactivity, and a cognitive process with a narrow yet excessive focus, as is the case with somatic preoccupation (which M manifested as he hyperventilated and went into a PNES episode, and which he also manifested through other symptoms outside of the specific PNES episodes). Therefore, PNES represent one symptomatic expression that occurs in the context of a disrupted arousal system. Such disruption can be due to a variety of neurobiological factors (e.g., the chronic administration of stimulant medication), psychological factors (e.g., recurrent traumatic and adverse experiences), and social factors (e.g., the reinforcement generated by the anxious response to symptoms by school and relatives not familiar with the condition).

M received care in different settings, which skillfully integrated school and family in their treatment plans. The involvement of these other social systems helps reinforce the skills learned in the treatment program and also prevents symptom reinforcement. Some specific technical aspects of the described intervention are worth highlighting as pivotal in treatment effectiveness. First, the use of a "physiological" explanation helped M understand and take charg of his treatment. It is common for providers to get stuck in trying to get patients to "accept" the "psychological basis" of their psychosomatic illness. Explanations based on mind-body integration not only help patients to accept their diagnoses more readily but also make them active participants in their treatment.

Second, the skills training targeted the underlying mechanism of M's symptoms—namely, his chronic state of hyperarousal—rather than each isolated symptom at the time of occurrence (i.e., each PNES event, each episode of hyperventilation). In other words, the goal of treatment goes well beyond symptom elimination. The goal, instead, is to create an underlying optimal arousal state that makes the patient less vulnerable to the development of symptoms. This was done by a mixture of breath retraining and of grounding and mindfulness skills that were practiced on a regular, scheduled basis. We have described a similar therapeutic approach for adults with PNES using a mindfulness-based protocol that featured regular practice of skills.[22]

Finally, the team recognized the need to revise treatment as the patient faced new challenges and stressors, including the possible onset of a bipolar disorder. Patients with PNES commonly have chronic, recurrent presentations.[23] Ongoing accessibility to treatment providers—to boost and update previously learned skills, make periodic assessments for comorbidities, and provide fitting environmental changes—is essential to minimize the functional impact of these periodic symptomatic exacerbations.

[2] Consultant 2

In this case history, an illustrative example of pediatric psychogenic non-epileptic seizures (PNES) is presented in a 14-year-old boy who has a personal history of developmental delay and multi-domain cognitive difficulties that include deficits in processing speed, attention, and abstraction. His history is also notable for past sexual abuse and chronic bullying at school, and he has a family history of anxiety, depression, bipolar disorder, alcohol misuse, intellectual disabilities, and migraines in first- and second-degree relatives. In this context, the patient unfortunately develops a spontaneous subarachnoid hemorrhage resulting in an intensive care unit admission and subsequent elevated intracranial pressure, hydrocephalus, headaches, and the need for multiple neurosurgical interventions. Following the above series of interventions, the patient became preoccupied with details related to his past hospitalizations, and he experiences intrusive thoughts and hyperarousal. The patient goes on to develop an additional headache syndrome, paroxysmal hyperventilation, and pain and tension in his neck framed as medically unexplained somatic symptoms. His symptom complex culminates in the manifestation of seizure-like events triggered by hyperventilation; an EEG obtained during a typical event provoked by instructed hyperventilation failed to demonstrate epileptiform activity.

This case history highlights the complexity of predisposing, precipitating, and perpetuating factors that are frequently found in patients with PNES[24] and related functional neurological symptoms.[25] Predisposing factors to the development of functional neurological symptoms in this case include the patient's personal history of developmental delay with cognitive symptoms, a family history of mood-anxiety symptoms and maladaptive coping behaviors (alcohol misuse), and previously experienced psychological stress, including sexual abuse and bullying. While pediatric PNES has been understudied to date, intellectual disability in adult patients is associated with PNES,[18] and intellectual disability has abeen

associated more broadly with the development of medically unexplained somatic symptoms.[26] In addition to cognitive difficulties, difficulties with verbal expression of emotion (alexithymia) is commonly also seen in many patients with intellectual disability, and alexithymia is a known risk factor for functional neurological symptoms.[27,28] The patient's endorsements of past sexual abuse and interpersonal difficulties with classmates are also significant predisposing factors to the development of PNES. In addition to high rates of past trauma, including sexual abuse (~30%) and physical abuse (~25%)[17,29] as noted by consultant one, individuals with PNES have been reported to exhibit earlier onset of events, greater diagnostic delay, more severe convulsions, and more emotional triggers and traumatic recollections.[30] The emergence of other medically unexplained symptoms in individuals with PNES has been connected to antecedent trauma.[17]

Precipitating factors to the development of PNES in this case include unexpected medical illness (spontaneous subarachnoid hemorrhage with multiple medical complications) and the development of PTSD. In the context of the cognitive and emotion-processing vulnerabilities discussed above, the patient develops recurrent hyperarousal; intrusive, negatively valenced thoughts related to his past hospitalizations; and fear of recurrent neurologic events. In addition, headaches come to trigger cascades of cognitive and emotional symptoms, including hyperarousal (with hyperventilation) and thoughts of dying. Hyperventilation is a known feature of some PNES subtypes. In an analysis of clinical characteristics associated with 75 PNES events in a pediatric population, hyperventilation was associated with nearly 20% of all non-epileptic events and 50% of asynchronous major-motor PNES events.[31] It is also important to highlight that hyperventilation is a frequent trigger for PNES in adults and that it is commonly used as an accepted provocation technique.[32]

This case presentation also illustrates important perpetuating factors commonly seen in patients with functional neurological symptoms. In particular, the patient's outside therapist is reported to favor a diagnosis of epilepsy, whereas the patient's medical and neurosurgery teams characterized the patient's symptoms as functional (psychogenic) in origin. This discontinuity exemplifies a commonly encountered problem—namely, that mental health professionals are frequently uncomfortable in caring for patients whose chief complaint is physical. It has been reported, for example, that psychiatrists compared to neurologists more frequently question an EEG-confirmed diagnosis of PNES.[33] As in this case, disagreements among care providers often lead both to uncertainty in the diagnosis and to poorly coordinated outpatient treatment plans. In this case the patient initially had difficulty understanding the nature of his PNES events and other functional symptoms, as well as difficulty appreciating associations between affective symptoms, arousal, and physical symptoms. Diagnostic delay and lack of acceptance of the diagnosis have been linked to poor prognosis (and thus symptom perpetuation) in PNES.[34] Here, the patient's intellectual disability may be framed as both a predisposing factor and a perpetuating factor.

Given the paroxysmal nature of the patient's PNES, it is worth noting the recognized association between PNES and panic attacks. Both PNES and panic attacks can present as paroxysmal crescendo events comprising somatic sensations that may seemingly be untriggered by a clearly recognized stressor and affective symptoms may be underappreciated by some patients during initial symptom onset.[35] An early study comparing 15 patients with PNES to 32 individuals with panic attacks showed that 70% of PNES subjects experienced a majority of panic attack symptoms during events.[36] Interestingly, patients with panic disorder may also endorse focal neurologic symptoms during their panic attacks.[37] In a retrospective analysis of 224 patients with PNES and 130 individuals with epileptic seizures, panic attack symptoms—including shortness of breath, heart palpitations, sweating, choking feeling, chest

discomfort, dizziness/unsteadiness, derealization or depersonalization, fear of dying, paresthesias, and chills or hot flashes—were more frequently endorsed during PNES than during epileptic seizures.[38]

While a detailed review of the neurobiology of PNES and related functional neurological symptoms is beyond the scope of this article and is available elsewhere,[28,35,39,40] select neuroimaging studies are highlighted here to aid a neurobiological understanding of the intersection of arousal and seizure-like events in this case presentation. Structural magnetic resonance imaging studies in PNES have demonstrated volumetric changes in multiple paralimbic cortical regions, including the anterior cingulate cortex and the insula, as well as atrophy in motor and premotor brain regions.[41,42] Resting state functional connectivity MRI studies have appreciated increased coupling between corticolimbic regions (e.g., anterior cingulate cortex, insula) and neural networks implicated in cognitive control and motor behavior.[43] In a study probing insula subregion connectivity, 18 patients with PNES compared to 20 healthy controls showed increased resting-state functional connectivity among the left ventral anterior insula, left post-central gyrus, and bilateral supplementary motor area.[44] In that study, the strength of connectivity between the left ventral anterior insula and the bilateral supplementary motor area positively correlated with non-epileptic seizure frequency. In a study of 18 patients with PNES, a similar positive association was observed between event frequency and increased coupling of anterior cingulate cortex and supplementary motor area activity.[45] These studies highlight categorical (PNES vs. healthy controls) and within-group symptom-severity associations between motor regions and paralimbic brain areas, suggesting that abnormal interactions across these networks may play a role in the pathophysiology of PNES.

Emerging roles for the anterior cingulate cortex and the insula in the biology of PNES and related functional neurological symptoms are particularly noteworthy, given that these

brain areas are convergent zones for the processing of viscerosomatic, cognitive, and affective information.[28,46,47] In the context of a distributed network biology, alexithymia[48] and dissociation[49] have also been linked to functional abnormalities in the anterior cingulate cortex. While the biological and psychosocial factors contributing to the development of PNES are complex and multifactorial, it is notable that basic science and human studies converge to demonstrate that aberrant neuroplastic changes following chronic stress exposure occur in corticolimbic regions, including the anterior cingulate and insula cortices.[50,51] Maladaptive functional and structural changes in multimodal integration regions mediating the convergence of affective, viscerosomatic, and cognitive processes contribute to the biology of functional neurological symptoms, though research is needed to replicate and build on early findings in the field.

[2] Consultant 3

The case of M is an excellent illustration of the presentation and management of a young man with complex and multiple psychosomatic co-morbidities and vulnerabilities. It highlights the crucial importance of careful history taking and of the mental health examination, as well as of the coordinated use of a variety of treatment resources. It raises issues about the medical management of these problems.

This commentary addresses the nature of this case's psychosomatic and psychiatric complexity; links between anxiety, hyperventilation and non-epileptic seizures; vulnerability factors and treatment. But first it considers the medical management of pediatric psychosomatic problems.

[3] The medical management of pediatric psychosomatic problems

M was referred to the psychological medicine service after he had made 11 visits to the emergency department over eight months; headaches and, later on, PNES were the most prominent presenting features. These symptoms had developed following recovery from three episodes of critical illness and neurosurgery. They had led to physical investigations with negative results, but he was only referred to pediatric psychological medicine after he developed hallucinatory phenomena, which in fact were simple and not suggestive of psychotic states.[52]

M may well have benefited from an earlier referral to psychological medicine. Critical illness is a highly stressful event that generates posttraumatic stress and other psychiatric disorders in a substantial number of children and young people.[53] Moreover psychiatric comorbidities are present at some point in the majority of child pediatric presentations with impairing functional somatic symptoms and somatoform/conversion disorders.[19,54,55] Early psychiatric screening by pediatric teams may have been expected to reduce the time over which symptoms escalated and became entrenched.

Unfortunately, referrals to psychological medicine of children with psychosomatic disorders tend to be delayed and unnecessarily costly, both psychologically – in terms of the suffering and disruption involved - and financially, and even in hospitals with available pediatric liaison child adolescent mental health or psychological medicine services, referrals contain little in the way of relevant psychosocial information.[56,57] This situation clearly needs improving.

[3] Multiple psychosomatic and psychiatric comorbidities; anxiety/ hyperventilation/ PNES

Because they occur at the intersection of physical and mental health, impairing psychosomatic disorders are in themselves clinically complex. In this case, the complexity was compounded by the multiple psychosomatic and psychiatric comorbidities, and by the extensive biopsychosocial vulnerability.

In M the neurosurgical disorder was a direct trigger for both the functional neurological symptoms—headaches, seizures, and accompanying somatic symptoms—and for the multiple comorbid psychopathologies, with symptoms indicative of PTSD, of generalized anxiety disorder and of panic disorder. This was moreover compounded whilst M was under psychiatric treatment by brief bipolar hypomanic episodes. In effect, his problems mirrored the multiple and interrelated pathologies seen in some children seen in pediatric specialist services, and they needed – as provided - a similar level of specialist psychiatric and mental health expertise.

Most compellingly psychosomatic in this case was the direct link between anxiety/panic/hyperventilation and the non-epileptic seizures observed by the expert psychiatric team. This close and demonstrable mental/somatic connectivity is uncommon in psychosomatic work, but it is a welcome reminder of the general and preeminent importance of anxiety for functional, somatoform/conversion and related disorders in children,[19,54] and of the need for clinicians to consider hyperventilation as a contributing factor in children with PNES.

This vigilance is especially called for because hyperventilation attacks do not appear to be commonly reported in neurological clinics, nor among child psychiatric referrals. In a study of 223 children admitted to a tertiary epilepsy center with difficult-to-treat paroxysmal events, amongst the 40% who did not have epilepsy only 3% had hyperventilation attacks.[58] Of 105 pediatric inpatients referred to a child psychiatry unit with conversion reactions and a broad range of functional symptoms, hyperventilation was present in 4%,[59] although higher

rates have been reported in children with PNES.[31] Hyperventilation is especially linked to panic disorder, where it is seen as critical for both the generation of somatic symptoms and the development of clinical anxiety; a possibly relevant biological mechanism is suggested by the fact that the capacity to normalize pCO2 levels when hyperventilation stops is thought to be compromised in patients with panic disorder.[60]

The biopsychosocial risks in M are likely to have contributed to the progression from hyperventilation-linked symptoms to PNES. Children with pediatric PNES differ from their siblings in three major respects. First they have significantly higher rates of lifetime adversities and medical illness. Second, they have more psychopathology, including PTSD and anxiety disorders. Third, they tend to adjust poorly to stress, as evidenced by fearful misinterpretation of physical sensations and by passive, deficient emotion-regulation and problem-solving/coping skills.[1,19]

In uncovering the links between anxiety and hyperventilation with altered CO2 levels and non-epileptic seizures, the clinical psychiatric assessment was a model of good psychological medicine/pediatric liaison at work, not only because this clarified the clinical picture of an uncommonly seen problem but also because it guided management and provided a plausible explanation for the child's symptoms, which contributed to his engaging with treatment. Making biological/psychological connections explicit to children and families at a carefully judged stage in treatment can be helpful in psychosomatic problems.

[3] Vulnerability factors

The severity and intricacy of this young man's clinical picture may be accounted for, in part at least, by the premorbid vulnerabilities. These involved (1) neurodevelopmental dysfunction, with ADHD, cognitive deficits, and chromosome abnormalities, (2) family and

possibly genetic psychiatric load, via a family history of ADHD, anxiety, alcohol abuse, depression, and bipolar disorder, and (3) psychosocial risks (e.g., a troubled household, history of bullying, and one episode of sexual molestation), alongside ongoing concerns about school achievement. In combination, these factors would have rendered M highly vulnerable to developing psychiatric comorbidity in response to acute stressors such as his recent and complicated medico-surgical history.

Clinicians may not always appreciate the extent to which children with severe functional symptoms are affected by concerns about school adjustment and performance and their lives compromised by their failure to attend school regularly.[57] In M, a young man with background cognitive limitations and a history of bullying, preoccupation with school performance was a recurrent theme, and it must be assumed that the school support provided as part of his in-patient treatment and the move from school to a life-skills program—enabling him to attend school, gain work experience, and obtain school reports based on his performance rather than examinations—would have contributed substantially to symptom abeyance.

[3] Treatment

The case history illustrates important aspects of treatment. (1) S First, since some children with functional somatic symptoms are reluctant to engage in psychological treatments, reaching a common ground with them is paramount. Second, when anxiety or other psychiatric symptoms reach a certain level of severity, psychological treatments can be difficult to institute until the ongoing arousal is reduced and contained through the use of psychotropic medication. Third, it may not be practical or feasible to institute treatment of such complicated cases in out-patient clinics. The in-patient approach may also be necessary

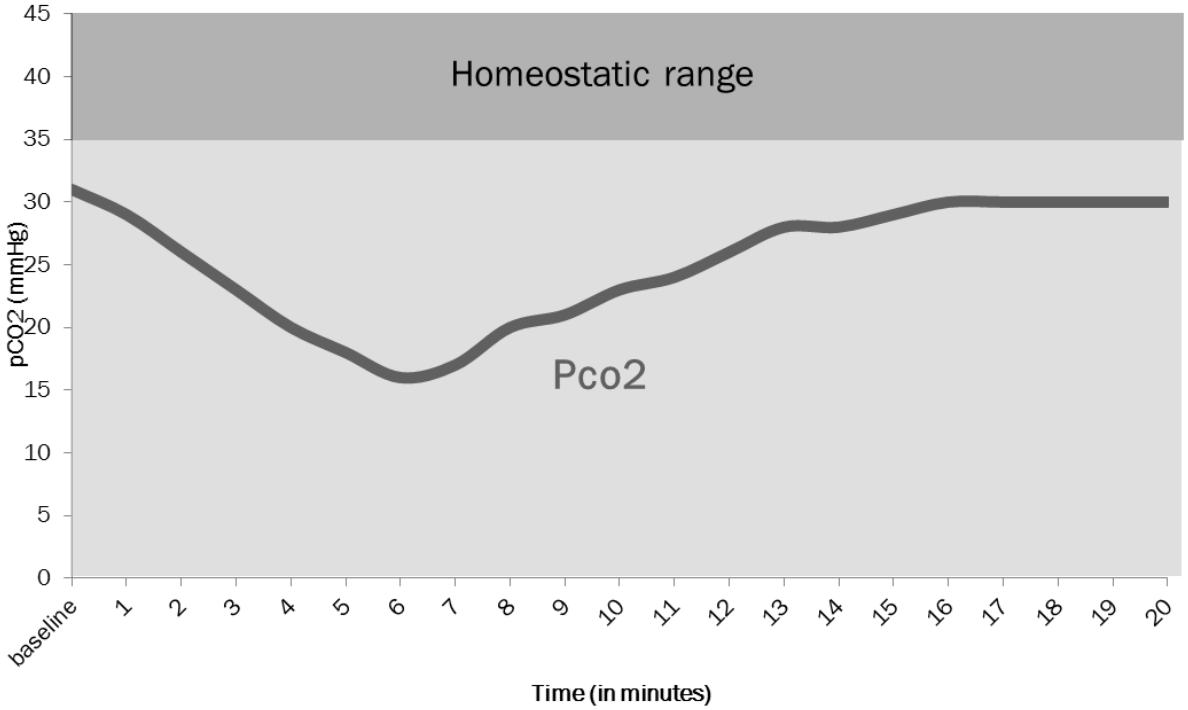
to monitor and manage the use of psychotropic medication efficiently, especially in young people who are multiply vulnerable and psychopathologically affected. In M's case, side effects needing attention included the impact of methylphenidate on heart rate, the associations between fluoxetine and elevated mood, and the possible effects of antipsychotics on weight gain. The usefulness of medical in-patient treatment for complicated child psychiatric cases has been well documented.[61]

Different professionals, with selective areas of expertise and sometimes opposing views can be involved with psychosomatic presentations. In M's case, the fact that the psychiatric/psychological medicine service took responsibility for case management, in consultation with others involved, was clearly key to understanding and managing the problem to resolution.

[3] Prognosis

Particular positive aspects of this young man's and his family's functioning may be expected to have facilitated the good response to treatment—most notably, his mother's early acceptance of a psychological contribution to the physical symptoms and M's own ability to make good relationships and work therapeutically with in-patient staff. Through the intervention, he learned psychological techniques for managing psychosomatic symptoms and anxiety; other symptoms were controlled with psychotropic medication; and educational supports were put into place to assist with his educational performance anxiety. This should help him navigate future stresses better. He remains vulnerable to future psychopathology under stress, however, and little is known about the adult outcomes of young people with severe psychosomatic presentations and multiple comorbidities—an important topic for future research.

Figure 1. Hyperventilation challenge done during M's hospital assessment


Homeostatic range
Pco2
pCO2 (mmHg)
45
40
35
30
25
20
15
10
5
0
baseline
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
Time (in minutes)

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