



A broader perspective: Functional symptoms beyond Neurology

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Introduction

A functional neurological disorder (FND) is one of the most common disorders seen by neurologists [44]. It is diagnosed by symptoms in patients with altered neurological function where another neurological disorder cannot explain the symptoms. The burden of FND is high, including increased health care costs [42], decreased quality of life [46], increased stigma [40], caregiver burden [25], and even death [35]. Many patients with FND also have other chronic medical disorders, including some that are also considered to be functional. Patients may receive different labels and explanations depending on where they are referred, the interests and knowledge of the clinicians seen, and the current understanding of the disorder. Longer symptom duration and comorbid psychiatric disorders have been associated with worse outcomes [16]. Lack of communication and understanding of other disciplines, as well as lack of clinician ownership may contribute to poor prognosis. However, the medical system has thus far not been tracking patients as if these functional disorders are related. This article introduces the more common non-neurological conditions currently believed to be functional, and how they are identified.

Suspecting functional symptoms

The suspicion for functional symptoms often begins with lack of response to conventional treatment or inability of the physician to detect abnormalities during routine medical investigations. The patient description of symptoms is extremely valuable, as it often uncovers atypical features. Other “red flags” include symptoms out of proportion to findings or inconsistencies during direct observation, and questionable coexisting diagnoses. A complete review of systems, and the psychosocial history can also provide clues for a functional etiology. Mental status examination, including affect and level of concern, may or may not be useful [4,27,39]. Other features may include limitations that seem to be beyond the observed manifestation of their symptoms. The physical examination can be very revealing. For example, in neurology, certain findings are strongly suggestive of functional etiology: Hoover sign for leg weakness, hemisensory loss for all modalities to midline, Romberg’s test with patient falling toward, and give-way

weakness [39]. Occasionally financial gains or other benefits may lead the clinician to suspect non-organic causes, but these may be better viewed as perpetuating factors.

Review by specialty

Gastroenterology

Gastroenterology may represent the most well described taxonomy of functional disorders, and due to their prevalence, general internists are likely to encounter them. The Rome criteria have described functional abdominal disorders and criteria for diagnosis since 1988 [12]. These conditions can be associated with any of the following: motility disorders, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, and altered CNS processing [12]. Generally, the diagnosis of “functional” disorders remains a diagnosis of exclusion, ie no structural abnormalities or major pathology can be identified by endoscopy, imaging, and serologic testing. There are many described entities, essentially encompassing the entire gastrointestinal tract [12]. Irritable bowel syndrome (IBS) is the most recognizable of these conditions and is characterized by abdominal pain related to change in bowel habits. Other common functional symptoms include globus (sensation of lump or tightness or particle presence in the throat), heartburn or reflux hypersensitivity (persistent pyrosis without evidence of gastroesophageal reflux disease, motility impairment or structural issue), dysphagia (sensation of difficulty swallowing), dyspepsia or upper abdominal pain syndrome, belching disorders, nausea and vomiting disorders (includes cyclic vomiting), rumination syndrome (repeated regurgitation of recently swallowed food without evidence of obstruction), constipation, diarrhea, gallbladder and biliary sphincter of Oddi disorders (repetitive abdominal pain in classic biliary colic pattern and location without evidence of obstruction or gallbladder disease), fecal incontinence and anorectal pain syndrome.

The approach to these patients depends on severity of symptoms, impact on quality of life, epidemiological factors, and co-existing conditions. It is estimated that 1 in 4 persons in the United States experience a functional gastrointestinal disorder at some point in their lifetime [38]. This accounts for approximately 40% of gastrointestinal problems seen by physicians yearly [37].

Patients with mild symptoms have maintained quality of life, non-disabling, and intermittent symptoms. These patients should

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receive empathetic, patient-centered listening and then be reassured that alarm features are not present and watchful waiting is often appropriate. The very real manifestations the symptoms do have on patients and the accepted general pathogenesis of gut-brain hypersensitivity should be carefully explained so as not to minimize impact. Treatment strategies may include engaging patients with food diaries and trial elimination of common triggers, e.g. lactose, gluten, fermentable olig-, di-, and monosaccharides, polyols, caffeine, fatty food and alcohol [12].

Patients with moderate symptoms experience intermittent disruption in their activities of living and decreased quality of life. Use of symptom diaries may be beneficial in patient engagement as well as elucidating temporal and causal factors. Empiric short courses of acid reducing medications are safe and cost-effective in patients with appropriate symptoms, e.g. pyrosis, waterbrash, eructation, upper abdominal pain syndromes. Limited use of non-opioid analgesics can be considered but length of therapy and possible complications should be carefully weighed and therefore non-steroidal anti-inflammatory drugs (NSAIDs) are generally discouraged [12]. If patients are inclined or recognize that psychosocial stressors play a role in triggering symptoms then referral or education regarding cognitive based therapy (CBT) and relaxation/mindfulness training can be useful [12].

Patients with severe symptoms represent the majority of those who seek multiple providers and hospital-based care. Given the severity of the impact these conditions have on quality of life, a diagnostic approach is indicated. Gastrointestinal imaging, empiric serologic testing for pancreatic, liver and biliary diseases, complete blood counts, and often endoscopies, are typically required. If, after a thorough evaluation, a functional disorder is suspected, quality education to the patient is needed along with clear description of putative pathophysiology. Patients are often treated with antidepressants, specifically tricyclic antidepressants (TCAs) and selective norepinephrine re-uptake inhibitors (SNRIs), which may also help with coexisting depression or anxiety [12]. Literature reviews have consistently shown benefit with the use of TCAs, SNRIs, and even hypnotherapy in the treatment of these patients [57]. Careful explanation of the dual impact of these medications on modulating brain hypersensitivity as well as effects on depression and anxiety is critical for patient compliance and therapeutic relationship with physician.

Interestingly, functional magnetic resonance imaging of the brain during inflation of balloons in the anorectal canal have demonstrated hyperactivity in the insular cortex, prefrontal cortex, and thalamus in patients with irritable bowel syndrome (IBS) compared to controls [49]. Given the similarity of these findings with neuroimaging studies of the various FND subtypes, there may be a common neurophysiological mechanism underlying all functional disorders as the brain is involved in everything.

Rheumatology

Pain is by definition subjective, and as such may be the most difficult symptom for which to prove a functional origin. In addition, the brain is by definition involved in pain [28]. Fibromyalgia is a common, important and controversial functional disorder. It is characterized by the enhanced sensitivity to a wide array of stimuli as well as mechanical pressure [8]. There are associated features of subjective cognitive impairment, depression, and, sleep disturbances. The hallmark of the condition widespread pain. A survey in the United Kingdom demonstrated 15% of the population reported chronic widespread pain with no specific diagnosis [14]. Though previously required, the validation with a certain number of triggers is no longer necessary. There are no specific tests to confirm the condition. A thorough history and physical is essential and some basic labs to ensure there is no myopathic or inflammatory

condition (complete metabolic panel and erythrocyte sedimentation rate) is reasonable; an extensive diagnostic algorithm is rarely indicated. Specifically, routine ordering of lupus antibodies or additional autoimmune markers is generally not recommended without other hallmark features of those conditions [2].

Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is characterized by prolonged, significant decrease in function, fatigue, post-exertional malaise, unrefreshing sleep, difficulties with cognition and information processing, and orthostatic intolerance [22]. Symptoms should be present for at least 6 months and have significant impact on functioning and quality of life at least half the time. A thorough history and physical is essential as fatigue is a protean manifestation of a wide array of medical conditions. If there are no other associated symptoms or physical findings that suggest a specific etiology then complete blood counts, complete metabolic profile, thyroid-stimulating hormone and muscle enzyme testing is a reasonable, limited evaluation. This is essentially a diagnosis of exclusion but extensive specialty testing and referrals are generally not indicated [22].

Psychogenic fever is an additional functional disorder that can exist independently or accompany fibromyalgia or CFS/ME. It is defined by increase in core body temperature related to a physiologic or emotional stressor in the absence of infection or systemic disease [36]. Given that fever is a heralding sign of acute and chronic conditions that warrant further investigation, e.g. infections, blood clots, malignancy, etc., this is a diagnosis of exclusion. Psychogenic fever often requires volitional actions and therefore may be more likely to be (or overlap with) factitious or malingering than functional.

Cardiology

Non-cardiac chest pain is very common and is a significant public health issue resulting in diminished quality of life and high healthcare utilization, especially in the acute setting. After a comprehensive assessment and prudent evaluation of potentially life-threatening issues has been undertaken, clinicians should counsel patients regarding the contribution of neuropsychiatric mechanisms and other mental health factors to chest pain. Most patients will hear “stress” and “anxiety” as dismissive to their physical health concerns, so caution is suggested to not blame the patient when testing is unrevealing. Referral to mental health clinicians may be beneficial to look for underlying conditions provoking or perpetuating the symptoms [58].

Chest tightness, difficulty in breathing and fatigue accompany depression and anxiety conditions among a myriad of others. Loss of consciousness and sudden collapse are often attributed to a cardiac etiology. However, they may be a manifestation of a neurologic condition, such as seizure or vertebrobasilar insufficiency, or a functional condition, such as psychogenic pseudosyncope. Syncope is another common presentation of a functional disorder and may present to different specialists, often cardiologists and neurologists. If captured during a tilt-table testing or video EEG monitoring, there are distinguishing changes on the EEG that are not epileptic [6]. Careful observation of autonomic signs (sweating, heart rate, blood pressure) during tilt table testing or other induction maneuvers can also help to differentiate functional from cardiac syncope, as in the latter ictal decrease in heart rate/blood pressure are expected while usually increase heart rate is seen at onset of functional syncope [21]. Based on the severity of symptoms, and critically the epidemiology as well as coexisting conditions, a thorough cardiac evaluation is often necessary when evaluating patients with symptoms which may be cardiopulmonary in nature. Any form of exertional chest pain or dyspnea, progressive symptoms, loss of consciousness or near syncope, or

symptoms of congestive heart failure should prompt a diagnostic plan to exclude life threatening etiologies [41].

Basic EKG is a must for any cardiac symptoms, and prolonged studies (Holter or loop monitors) can be useful. Echocardiogram, stress-testing and possible tilt-table testing may be warranted based on risk factors and symptoms.

Urology

Erectile dysfunction is a commonly reported condition, especially in men over the age of 40. Epidemiological research indicates that as much as 43% of men report erectile dysfunction, and a correspondingly higher percentage experience it as age increases Lindau et al. [60] Aug 23. Erectile dysfunction has numerous organic contributors which should be considered when evaluating patients. Furthermore, sexual function relies on a complex interaction between physiologic and emotional or mental factors and multiple contributing etiologies may occur simultaneously. Patients should be evaluated for cardiovascular contributions (e.g. peripheral vascular disease, diabetes mellitus), endocrinology pathology (e.g. hypogonadism, hyperprolactinemia), penile and prostate factors (e.g. Peyronie disease, prostatic hypertrophy), and medication contributors (e.g. antidepressants, antihypertensives, recreational drug use) [55]. Depression screening, complete blood count, free testosterone level, lipid panel, hemoglobin A1c, and thyroid function testing are all indicated in the initial evaluation [55]. Vascular ultrasonography is increasingly used as part of the diagnostic algorithm in identifying cardiovascular causes as well as a modality of treatment [54]. If no organic etiology is found it is likely the patient has a psychogenic or functional erectile dysfunction.

Pulmonary; Allergy, Asthma, and Immunology

Cough is the most common presenting complaint of patients in the primary care setting and chronic cough of 8 weeks or greater is a significant burden [11]. There are many proposed diagnostic algorithms to approach this situation as the putative etiologies are numerous. In general, further diagnostic testing and therapeutic challenges are indicated for chronic cough. Studies have demonstrated that asthma is the most commonly elucidated cause, perhaps as much as 24%, when investigation is undertaken [26]. GERD and upper airway cough syndrome, commonly referred to as post-nasal drip, are the two other most likely etiologies.

A thorough history and physical examination is the most important first step in evaluating chronic cough. The temporal nature of the cough, relationship to activities or settings, associated additional symptoms, medication usage, personal and family history of atopy, smoking history, exposure and occupational history are all critical historical components in assessing this condition. If there is no clear association from initial discussion and examination, there is heterogeneity regarding which steps should be taken. It is reasonable to obtain routine chest radiography, complete blood cell counts with differential to assess for eosinophilia, and pulmonary function testing [32]. It should be noted that cough variant asthma may elude detection with routine pulmonary function testing due to the variability in lung function inherent to the disease [18]. Therefore, repeat testing may be indicated. Absent any specific features, a trial of inhaled corticosteroid (ICS) with or without inhaled long-acting beta-agonist (LABA) is a safe and rational intervention [32]. There has been suggestion that patients with reflux of non-acid fluids or patients without typical GERD symptoms may have under-recognized reflux-induced cough. It has been reported in small studies that chronic cough improved greatly with reflux related surgery despite failure to demonstrate acidic esophageal pH prior to procedure [23]. However, without

clear signs or symptoms of GERD, it is not generally recommended to trial acid suppression with antihistamine or proton-pump inhibitor (PPI) therapy [24].

Bronchoscopy or laryngoscopy, high resolution computed tomography (HRCT), methacholine challenge, and acid-fast bacilli testing may all have a role. The diagnosis of idiopathic cough or somatic cough syndrome can only be considered once this work-up has been completed, illustrating again a diagnosis of exclusion.

Otorhinolaryngology

Vocal cord dysfunction may cause chronic cough. It is commonly misdiagnosed as asthma in patients who report shortness of breath that is variable. Vocal cord dysfunction refers to the finding of paradoxical motion of the vocal cords during breathing. Patients are often treated for asthma with poor response for prolonged periods before diagnosis is reconsidered and re-evaluated. Laryngoscopy is indicated when this diagnosis is considered in the setting of poor response to asthma treatment or failure to demonstrate variable lung function or reversibility in pulmonary function testing. Patients with vocal cord dysfunction as well as chronic idiopathic cough have demonstrated laryngeal hypersensitivity with quantitative sensory testing: capsaicin cough reflex sensitivity, hypertonic saline challenge, the timed swallow test, acoustic voice testing, cough frequency monitor and a voice stress test [48].

Nephrology

Functional or primary polydipsia is a cause of hyponatremia. In this condition, patients drink excessive amounts of solute-low fluids thereby diluting their plasma sodium concentration and osmolality. It is associated though not exclusively seen in psychiatric conditions such as schizophrenia as well as in patients with cognitive impairments and substance abuse. A thorough history is often the most essential means of making this diagnosis. If a history of excessive water intake is present, a deprivation trial and demonstration of sodium normalization is diagnostic. However, in the absence of this clear history, further diagnostic testing with complete metabolic profile as well as urine and plasma osmolality is indicated to determine the cause of the hyponatremia [56]. Because polydipsia often requires volitional actions (drinking water), it may be more likely to be (or overlap with) factitious or malingering than functional.

Gynecology

Symptoms that are relatively commonly found to be functional can be classified in different categories [7]. Pain presentations include chronic pelvic pain syndrome, vulvodynia, mastodynia, and pain due to a urethral syndrome. Urgency-frequency syndrome (aka overactive bladder) and incontinence overlap with urology. Endocrine syndromes such as secondary amenorrhea, anovulation with or without poly-hypermenorrhea, functional hyperprolactinemia can also be functional. The diagnostic approach is characterized by a careful physical examination and tests that often demand imaging and multidisciplinary collaboration. Thus functional symptoms here again are basically a diagnosis of exclusion.

Dermatology

There are a variety of "skin picking" syndromes, of which some are functional [31,34,43]. The presentation is typically severe with chronic, subacute, and acute excoriations. The "picking" can also be related to delusions of parasitic infestations [43]. Pruritus can exist

without excoriations, thus being purely subjective, and presents a diagnostic challenge to classify as functional [9]. Again, in dermatology, a functional etiology is essentially a diagnosis of exclusion and requires a thorough examination, laboratory testing, and often a skin biopsy. The possibility of factitious disorder or malingering, rather than functional disorder, also exists.

Neurodermatitis also known as lichen simplex chronicus, is controversial and overlaps with other skin conditions such as eczema, so its definition and the role of psychological factors is unclear [10].

Ophthalmology

There is a surprising paucity of literature on functional or “nonorganic” visual loss (blindness). Unlike most other functional symptoms, it needs to be differentiated from malingering or factitious mechanisms, which may be more common [33,50,51,52]. A thorough eye exam and neuroimaging are required. Specific maneuvers can be very useful, such as the mirror test, confusing lenses test, and the Bravais test [33]. The optokinetic nystagmus response can also be useful, especially in the context of complete blindness. Another relatively common functional syndrome in ophthalmology is convergence spasm, which can be quite dramatic and relatively easy to identify clinically [17].

Neuropsychology/Cognition

Functional cognitive disorder (FCD) has received much less attention in the literature compared with other functional disorders. FCD complaints typically include “brain fog,” memory or attention difficulties, although word-finding errors and linguistic impairments have also been described. Historically, functional cognitive symptoms have remained largely unrecognized in mainstream medicine, probably due in part to the subjectivity of milder memory or attention complaints that are often categorized under general terms such as “mild cognitive impairment.” To date, FCD is unrecognized in the DSM of the American Psychiatric Association [1] where it is neither included under functional neurological symptom or neurocognitive disorder categories. Despite this, recent studies suggest FCDs represent at least one quarter of all referrals to dementia specialist clinics [30,29]. Fortunately FCD seems poised to join with other disorders under the FND umbrella [20] which will hopefully lead to more recognition and differentiation from organic dementias as well as development of specialized treatment [3].

Once objective signs of organic cause have been ruled out, the primary differentiation of FCDs from other traumatic or neurodegenerative causes is that patients will have symptoms that remain static or diminish over time, as opposed to gradual progression associated with age-related decline or organic deterioration. Early flags for FCD might also include the patient being much more aware of impairment than family or friends, with detailed symptom description during examination (the opposite tends to occur in organic presentations) [19]. The spectrum of cognitive impairment can range from minor annoyances to daily reduction in adaptive living skills that is quite severe [3]. Beyond this, formal cognitive and effort testing alone is likely to be insufficient at differentiating FCD from organic causes as objective deficits may or may not be present [29–30].

Most importantly, FCD displays internal inconsistencies within a cognitive domain (e.g. memory, attention), that may be evident through a number of clinical observation planes including paradoxical worsening with effort or divergence between subjective versus observed impairment [3]. The role of standardized cognitive testing then, may best be defined by helping establish baseline performance within specific cognitive domains that can then be com-

pared to other sources of information regarding inconsistent patient functioning in that area. Cognitive testing may also hasten narrowing down of differential diagnoses for cognitive complaints, including undiagnosed learning disabilities.

Various etiology subtypes likely share a final common pathway to FCD symptoms. These range from the typical executive functioning deficits accompanying major depression (slower speed of cognitive processing) and anxiety disorders (reduced working memory and attention) to the forgetfulness, distractibility and word-finding difficulties (“brain fog”) often described in a number of disorders including chronic fatigue and fibromyalgia [47]. In the case of psychiatric comorbidity, treating primary depressive or anxiety disorders should help to resolve temporary impairments. Psychoeducation about the impact of mood/anxiety disorders on executive functions is also important when reassuring patients. Similar metacognitive complaints are described across various FND subpopulations, including functional seizures and movement disorders and may represent a common neurobiological malfunction [13], [15;51].

Another subtype, termed “cogniphobia” by McWhirter and colleagues [29] describes a health anxiety etiology whereby excessive attentional focus on normal subjective experiences of cognition robs attentional resources and produces “metacognitive error” leading to overestimation of deficits. When coupled with increased worry about symptoms, excessive autonomic arousal can follow resulting in further drain of attentional resources and reinforcement of a negative bias towards one’s own abilities. Beyond psychoeducation, management in this case would best be served by cognitive behavior therapy targeting attentional bias towards symptoms, behavioral activation (to aid in reducing symptom focus) and behavioral or pharmacological approaches that help to promote self-regulation and reduce autonomic hyperarousal contributions in the above model. Temporary behavioral strategies and accommodations that help support more severe impairments (at work, school) may also be beneficial, as long as they promote recovery and do not reinforce adaptive deficits. Some examples might include scheduled behavioral activation (to aid in reducing symptom focus, autonomic arousal), use of memory aids to increase verbal/visual recognition and additional time when learning new information or procedures.

Conclusions

While there is much to be learned about functional disorders in medicine, it remains quite challenging to study them without understanding or tracking and managing the referral patterns within the health care system. As knowledge of the neurobiological underpinnings of physical and mental health symptoms increases, there is tremendous hope for improved outcomes that will benefit patients, clinicians and the entire health care system. There is much to be gained from communicating across specialties, with generalist and specialist working in concert with the patient to manage functional illness within an integrated care team across specialties. The non-neurological presentations of functional disorders will require further research so that they do not continue in the “rule out” everything else category, and earlier and more definitive diagnoses can be delivered with clear explanations and management. Education is needed within the integrated team which must include patients, caregivers, and families and all referring clinicians. It is important that functional disorders not be dismissed as “just stress” given their frequency and debilitating nature. They should be managed with a multidisciplinary approach, and ideally with a more active role on the part of mental health professionals [5].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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