Generalized Anxiety Disorder, Somatization, and Emotional Dysregulation: A Possible Link

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Abstract

In clinical practice, it is quite common to deal with patients who primarily express somatic symptoms. They can be distinctive features of depressive disorders, of anxiety disorders, in particular general anxiety disorder, and, less commonly, of somatic symptom disorders. Nonetheless, in several patients, these three conditions could coexist and delineate a clinical picture driven by emotional dysregulation (ED). ED is an emotional response to external stimuli that is poorly modulated and does not fall within the conventionally accepted range of emotive response, which can be characterized by marked and rapid fluctuation of mood, mood lability, weeping crisis, eating problems, and up to behavior outbursts. In our clinical case, a female patient came to our attention reporting headache, gastrointestinal disturbance, hyporexia, and leg restlessness. The diagnostic approach is pictured, and a correct pharmacological treatment is shown in this chapter.

Keywords

Generalized anxiety disorder · Somatization · Emotional dysregulation · Magnetic resonance

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12.1 Introduction

12.1.1 Generalized Anxiety Disorder

Generalized anxiety disorder (GAD) is a common mental health condition characterized by an excessive and persistent worry about everyday life with no obvious reasons and not restricted to particular circumstances. Physical anxiety symptoms (such as tachycardia, tremors, headaches, sweating, nausea) and psychological symptoms (including restlessness, fatigue, difficulty in concentrating, irritability, and altered sleep) represent characteristic key points [1]. A recent cross-sectional study conducted around the globe reported a 3.7% lifetime prevalence, being higher in high-income countries [2]. These data make GAD a common public health concern, particularly for females and older subjects that show an even higher prevalence. Moreover, associated functional impairment is reported to be similar to patients suffering from major depressive disorder. The course of the disorder is chronic, with poor family relationships, high rates of comorbid axis I disorders, and cluster C personality disorders that can worsen its evolution [3].

Box 12.1 Diagnostic and Statistical Manual of Mental Disorders 5 (DSM 5) Criteria for GAD

(A) Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).
(B) The individual finds it difficult to control the worry.
(C) The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 months) (Note: Only one item is required in children):
    1. Restlessness, feeling keyed up, or on edge
    2. Being easily fatigued
    3. Difficulty concentrating or mind going blank
    4. Irritability
    5. Muscle tension
    6. Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep)
(D) The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
(E) The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism).

(continued)

Box 12.1 (continued)

(F) The disturbance is not better explained by another medical disorder (e.g., anxiety or worry about having panic attacks in panic disorder, negative evaluation in social anxiety disorder [social phobia], contamination or other obsessions in obsessive-compulsive disorder, separation from attachment figures in separation anxiety disorder, reminders of traumatic events in posttraumatic stress disorder, gaining weight in anorexia nervosa, physical complaints in somatic symptom disorder, perceived appearance flaws in body dysmorphic disorder, having a serious illness in illness anxiety disorder, or the content of delusional beliefs in schizophrenia or delusional disorder).

As for other psychiatric disorders, GAD etiology is multifactorial with genetic and environmental factors playing an important role in its development. Among genetic factors, literature studies have reported that GAD tends to cluster in families, where a positive family history plays a role in increasing the likelihood to develop GAD. Twin studies have shown a moderate hereditary influence, which is, however, less intense than in other anxiety disorders, e.g., panic disorder [4]. Some genes associated with GAD are key genes implicated in the adrenergic nervous system, GABA, and serotonin pathways [5]. These genes might contribute to abnormal neuronal pathways, involved in cognitive functions like thinking and emotion. Functional MRI (fMRI) studies in GAD patients have identified abnormal amygdala and prefrontal cortex activation and decreased functional connectivity between these areas. Furthermore, additional studies showed increased gray matter volume and decreased structural connectivity between these brain structures [6]. Additionally, a recent review analyzed the role of proton magnetic resonance spectroscopy (^{1}H MRS) investigations in patients with GAD. This new technique has the aim of identifying differences in metabolite levels between conditions in key brain areas. As results, the majority of studies reviewed showed altered metabolite levels in the dorsolateral prefrontal cortex and hippocampus, suggesting regional specificity [7].

Among environmental factors, trauma and stressful life events, such as abuse, loved one's death, divorce, and changing jobs or schools, may contribute to the onset. Addictive substance use/withdrawal, including alcohol, can worsen anxiety symptoms and facilitate GAD development. Additionally, an association between smoking and anxiety symptoms has been reported, with a risk of GAD 5–6 times higher among adolescents who smoke heavily compared to nonsmokers [8].

12.1.2 Somatization, Somatic Symptom, and Related Disorders

Somatization is defined as a patient's concern about physical symptoms, occurring when someone tends to communicate psychological distress in the form of a somatic symptom. This tendency is common in the general population and can be considered

a worldwide phenomenon, more common in women and older ages [9]. When a significant functional impairment is associated, specific psychiatric disorders can be delineated.

DSM 5 collects these disorders under the diagnostic group of "somatic symptom and related disorders" that constitutes a new diagnostic category compared to DSM IV-TR. This chapter includes:

- Somatic symptom disorder (SSD), when patient symptom concern worries him/her constantly and/or drives him/her to see doctors frequently
- Illness anxiety disorder, when patients are excessively preoccupied and worried about the possibility of having or getting a serious illness
- Functional neurological symptom disorder (formerly known as conversion disorder), when physical symptoms resemble a nervous system disorder
- Psychological factors affecting other medical conditions
- Factitious disorder, when people pretend to have symptoms for no apparent external reason (such as to get time off from work)
- Other specified somatic symptom and related disorders
- Unspecified somatic symptom and related disorder

Patients suffering from somatic symptom disorder (SSD) report a significant concern about physical symptoms, with abnormal thoughts, feelings, and behaviors. Although medical conditions are excluded, excessive worry leads to frequent doctor visits, experiencing major emotional distress and difficulties in overall daily functioning. The SSD key point is that the patient feels and behaves in response to physical sensations and not only the symptom itself [1]. Studies report widely variable lifetime prevalence of SSD, varying from 0.2% to 2% for females and less than 0.2% for males [10]. However, SSD is particularly more common in primary care and other medical settings, with an estimated rate reported of up to 15.1% [11].

In relation to functional neurological symptom disorder, patients report different neurological symptoms (i.e. hemiparesis, paraparesis, monoparesis, alteration of consciousness, visual loss, seizure-like activity, pseudocoma, abnormal gait disturbance, aphonia or dysphonia, lack of coordination, or a bizarre movement disorder) with no medical explanation. Conversion symptoms are seen also in other clinical conditions like affective disorders, antisocial personality disorder, alcohol or drug abuse, or organic, neurologic, or medical illnesses. Other functional conditions such as irritable bowel syndrome, fibromyalgia, chronic pelvic pain, and multiple chemical sensitivity syndrome also have strong associations with conversion disorders.

This clinical picture was classically called "hysteria" derived from Hippocrates' "wandering" uterus. Freud developed this term, reconsidering the psychoanalytic concept of repression through "conversion" of psychological distress into a physical symptom. Recently, DSM 5 focused on brain function abnormalities and reconsidered the diagnostic category of conversion disorder into functional neurological symptom disorders. In this respect, recent studies have shown a possible neurobiological basis, with significantly smaller mean left and right amygdala

volumes, without any differences in total gray/white matter or hippocampus volumes in patients with conversion disorders [12]. Additionally, stronger connectivity values in the insula, inferior frontal gyrus, and parietal cortex and precentral sulcus were shown in patients with psychogenic non-epileptic seizures, a quite common presentation of this disorder [13]. Environmental factors also play a role in its pathogenesis; for instance, an immediate precipitating source of stress, such as divorce or loss of employment, may be associated with the development of the disorder. Moreover, a history of sexual or physical abuse is common among these patients and is reported in up to one half of patients suffering functional neurological symptom disorders [14].

Box 12.2 DSM 5 Criteria for Functional Neurological Symptom Disorder

(A) One or more symptoms of altered voluntary motor or sensory function.
(B) Physical findings provide evidence of incompatibility between the symptom and recognized neurological or medical conditions.
(C) The symptom or deficit is not better explained by another medical or mental disorder.
(D) The symptom or deficit causes clinically significant distress or impairment in social, occupational, or other important areas of functioning or warrants medical evaluation.

To correctly diagnose functional neurological symptom disorders, teamwork between a neurologist and a psychiatrist is mandatory. The psychiatric assessment can differentiate functional neurological symptom disorder from other somatoform disorders and factitious disorders and can elucidate the psychodynamic basis. On the other hand, the neurologist must recognize the nonorganic process and avoid potentially dangerous diagnostic or therapeutic interventions.

12.1.3 Emotional Dysregulation

Emotional dysregulation (ED) refers to an emotional response to external stimuli that is poorly modulated and does not fall within the conventionally accepted range of emotive response. ED might express itself with marked and sudden fluctuation of mood, mood lability, weeping crisis, eating problems, right down to angry outbursts or behavior outbursts such as destroying or throwing objects, and aggression toward self or others [15]. Differently from mood changes described in depressive or manic/hypomanic episodes, these variations usually occur rapidly, in seconds to minutes or hours. ED must be considered a psychiatric concern when its extent interferes with personal social interactions and relationships and causes a marked impairment in daily life [16].

Over 85% of diagnoses in the DSM involve excesses or deficits of emotions or a lack of coherence among emotional features [17]. In particular, ED is a core

psychopathological factor in psychiatric disorders such as bipolar disorder, major depressive disorder, borderline personality disorder, attention deficit hyperactivity disorder, posttraumatic stress disorder, and autism spectrum disorders. ED is common also in patients with somatoform disorder, alcohol and substance abuse disorder, and anorexia and bulimia nervosa [18].

Emotion regulation involves a set of processes and systems (e.g., attentional, cognitive, behavioral, social, and biological) that act to modulate, manage, and organize emotions in order to help individuals to meet environment demands and achieve their goals [19]. Different factors play a role in the genesis of emotions and the limbic system is one of the most important. Emotional experience involves the integration of visceral signals from the limbic cortices through the cognitive appraisal of these signals in the prefrontal cortex (PFC) [20]. In healthy individuals, cognitive reappraisal of emotion can occur through the top-down prefrontal regulation of limbic activity, using elaboration to modulate initially negative appraisals as being less negative. In mood disorders, however, this cognitive control seems to be impaired, as evidenced by altered connectivity between the PFC and limbic regions, in particular the amygdala. An important clinical implication of these findings is that in patients with a mood disorder, the process of regulating negative emotions may be maladaptive, as emotional information from the limbic system is not regulated by the prefrontal cortices. In confirmation of these hypotheses, neuroimaging studies reported atypically diffuse prefrontal recruitment in depressed patients both during cognitive task performance and during task-free protocols [21].

12.2 Clinical Case

12.2.1 Case Report

A.P. is a middle-aged woman, born in Central Italy, who came for the first time to our department in June 2015. She was brought to the ER of our hospital by her mother. At the psychiatric evaluation, she appeared cooperative toward the examiner. She had a normal state of consciousness, oriented in time, space, and person. Attention was maintained. She looked very agitated and tense and was crying and showing involuntary movements of legs and arms. She said that she had lately been excessively anxious and worried during most of the day at work and in her family life. Speech rate was increased and elevated in tone. Her mood was depressed and her affect was labile. She described the inability to express her feelings completely and clearly, with words such as “an interior chaos” dominating her emotions. Formally the thought was correct, with content focused on worries related to her depressed mood state and obsessions related to her body. She reported altered sleep, with approximately 4 hours per night in the last week, and her food intake was poor with nearly 5 kg weight loss in the last months. No alteration in perceptions was reported. She had no insight into her clinical condition. Due to the clinical picture, she was admitted to the psychiatric ward of our department.

Collecting patient's history, she reported a positive family history for psychiatric illness: a cousin was diagnosed with a major depressive disorder and committed suicide at the age of 70. Her mother, at that time aged 70, was described as a hyper-protective and anxious person, never treated by a psychiatrist. Her father, who left the family when the patient was 6 years old, was described as a violent person who committed crimes. In relation to patient medical history, no complications were described during pregnancy; however forceps was applied due to a delay in delivery procedure. She received regular breastfeeding, and no problems in somatopsychic development are reported. Menarche occurred at the age of 13 and menstruation was regular. She had neither abortions nor pregnancies. She never smoked and never took any recreational drugs/alcohol in her life. With regard to medical diseases, she suffered hypothyroidism, treated with levothyroxine. No allergies were reported. A low food intake was described, with several occasions of voluntary weight loss, without meeting the diagnostic criteria for anorexia nervosa. Personality was characterized by shyness, with few friends since she was prone to solitary activities. The mother has been a determining figure in the patient's life: described as hyper-protective, used to controlling every aspect of patient's life, from education to the relationship with her husband. During childhood the patient was frequently sick with episodes of fever and vomiting, and her mother was worried about her and therefore tended to limit her autonomy. As to education, she got a high school diploma with good results. She wanted to go to university, but her mother dissuaded her because she considered her daughter "too weak." So she began working in a call center which is the only employment she has had in her life, remaining till the age of 46. She got married at the age of 28, but the relationship was described as unstable with some violent episodes, and they separated when the patient was 46; they did not have any children.

From the age of 33, the patient started to report different concerns about physical symptoms: occasionally, she suffered from headache and nausea, with an associated decrease in food intake, and during sleep, she had the feeling of being unable to keep her legs still. For these concerns, she went to her general practitioner who prescribed symptomatic drugs. At that time, she could hold down her job and maintain an overall good functioning. A worsening of the clinical picture occurred when the patient was 36, with episodes characterized by extreme anxiety, anhedonia with clinophilia, altered sleep patterns with periods of hypersomnia and terminal insomnia, and akathisia. At that time, she had her first contact with a psychiatrist and started the first proper oral pharmacological treatment with amisulpride 100 mg per day, valproic acid 750 mg per day, and quetiapine 50 mg per day. Pramipexole was specifically prescribed for "restless leg syndrome."

Box 12.3 Restless Leg Syndrome

Restless leg syndrome (RLS) is a neurologic movement disorder of the lower limbs associated with sleep distress. Patients with RLS report an irresistible urge to move the legs that are not painful but are distinctly annoying. This happens typically during the night and may be associated with daytime tiredness and physical and emotional disability.

(continued)

Box 12.3 (continued)

The diagnostic criteria from the International RLS Study Group are:

- An urge to move the legs usually but not always accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs.
- The urge to move the legs and any accompanying unpleasant sensations that begin or worsen during periods of rest or inactivity such as lying down or sitting.
- The urge to move the legs and any accompanying unpleasant sensations that are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
- The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity that only occur or are worse in the evening or at night, rather than during the day.
- The occurrence of the preceding features is not solely accounted for as symptoms primarily due to another medical or behavioral condition such as myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, or habitual foot tapping.

All patients with symptoms of RLS should be tested for iron deficiency. If a secondary cause of RLS is suspected on the basis of history, abnormal findings on neurologic examination, or poor response to treatment, other laboratory tests should be performed. In-depth analysis includes needle electromyography/nerve conduction studies to exclude a polyneuropathy or radiculopathy and a polysomnography.

Drug therapy for primary RLS is mainly symptomatic, since cure is possible only in secondary disease. Medications used in the treatment of RLS include dopaminergic agents, benzodiazepines, opioids, anticonvulsants, presynaptic alpha 2-adrenergic agonists, and iron salt.

Nonpharmacological treatment, like sleep hygiene measures, avoidance of stimulants (caffeine, alcohol, and nicotine), and discontinuation of medications that cause or exacerbate RLS (such as selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, diphenhydramine, and dopamine antagonists), proved to have some benefits in RLS treatment.

With a proper pharmacological treatment, she reported a partial symptoms improvement; however she started to be focused on several side effects that she attributed to the medications, and for this reason, she voluntarily interrupted all drugs. A worsening in the anxious symptoms led to a first hospitalization in a private clinic at the age of 38. A treatment based on valproic acid 750 mg per day, paroxetine 10 mg per day, and clonazepam 2 mg per day was set. After discharge, a long period of wellness with only a few mild relapses followed till she was 43 years old. At that time, a second hospitalization occurred due to increased psychomotor agitation and

restless leg syndrome that the patient could not control, despite the correct consumption of pharmacological treatment. During hospitalization, she was treated orally with valproic acid 550 mg per day, trazodone 100 mg per day in combination with paroxetine 10 mg per day, and flurazepam 30 mg per day. She received a diagnosis of major depressive disorder comorbid with histrionic personality disorder. After discharge, the patient did not show stability in her clinical picture, a decrease in overall functioning occurred, with loss of employment and gradual social isolation. She used to stay at home and she began to be hyporexic, with lack of appetite. Moreover, she started to have bowel problems; her diet was based only on squashed fruit. A weight loss of 5 kg in the past months was noted. An increase in anxiety symptoms with distress, restlessness, and depressed mood without suicidal ideas occurred. The symptoms worsened till the patient came to the attention of our clinic in July 2015 and, due to her overall state, was admitted to our psychiatric unit, at the age of 46.

During the first hospitalization in our department, gabapentin 900 mg per day was added as second mood stabilizer, in addition to valproic acid, which was increased to 900 mg per day. Zuclopenthixol 20 mg per day was initially started, later substituted with aripiprazole 10 mg per day and also interrupted later on due to an increase of agitation and restlessness. Intravenous valproic acid 400 mg/day was then introduced. A second antipsychotic, chlorpromazine 75 mg per day, was added to control akathisia and the lower limb movements. Dothiepin 75 mg per day, a tricyclic antidepressant, was started to control the depressed mood. Levothyroxine was continued because of patient hypothyroidism.

To evaluate global neurological functioning, a brain magnetic resonance imaging (MRI) was performed (Fig. 12.1a) which reported: "Sulci and ventricles within the limits. No acute intraparenchymal alterations are observed. Non-specific minor signal alterations in the subcortical frontal region. Minimal cortical atrophy in frontal and parietal lobe. Hypoplastic trajectory of the left vertebral artery. Mucous cysts in the left maxillary sinus." A positron emission tomography (PET) (Fig. 12.2) was also performed: "Mild globally diffused reduction of the concentration of the tracer throughout the cortical hemispheres, most likely on a functional basis, but there

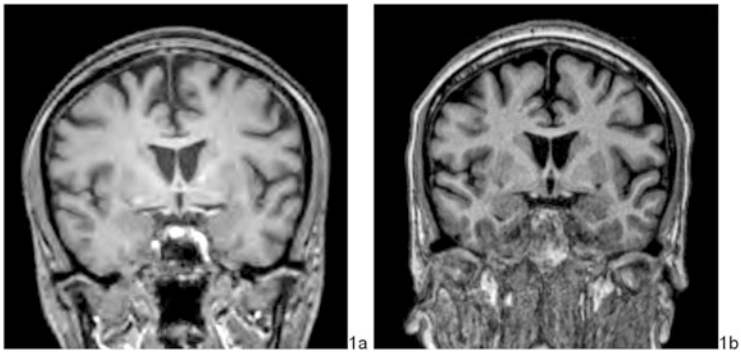

Fig. 12.1 (**a** and **b**) MRI performed in 2015 (**a**) and in 2016 (**b**)

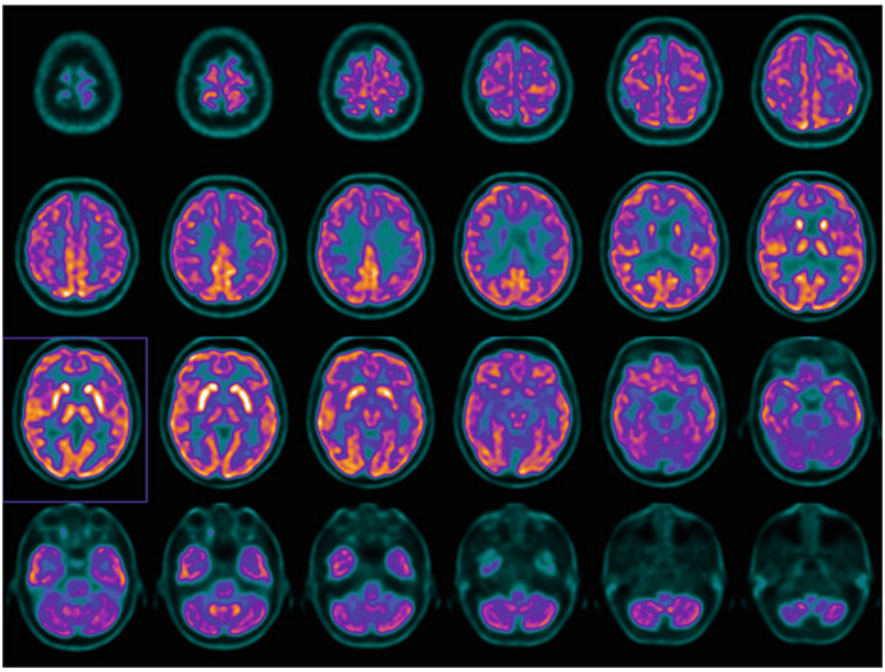

Fig. 12.2 PET performed in 2015

are no clear hypometabolic areas in examined cortical structures. The fixation of the tracer at the level of the examined subcortical structures (thalamus and basal nuclei bilaterally) is normal. In conclusion, PET study reported a glucidic metabolism globally maintained and therefore not suggestive of neurodegenerative aspects." Furthermore, an electroencephalogram showed "9–10 Hz background rhythm, good consistency, symmetrical, reagent, HP and SLI inactivated. In conclusion, EEG shows no significant specific abnormalities."

To evaluate global cognitive functioning, neuropsychological tests were performed and showed an 88 Intelligence Quotient. Speech and memory performances were within the limit, with a motor proficiency value at the lower level and a frontal proficiency evaluation under the lower limit. Lastly, a neurological evaluation was performed; the patient showed hypomimia and bradykinesia, with involuntary movement of the lower limbs. During the evaluation, an episode of involuntary movements of the lower limbs, with choreoathetosis characteristics, of the duration of a few seconds, without disturbance of consciousness, was described. No other neurological signs were depicted. The neurologist confirmed the overall decrease in the bilateral frontal functions with minimal atrophy in the frontal and parietal cortical regions seen in the MRI. In relation to the involuntary movements, the specialist concluded for a picture of ambiguous interpretation that requires a follow-up evaluation due to the effects of ongoing therapy.

To evaluate weight loss and bowel distress, a complete abdomen echography was performed and any organic diseases were excluded, as confirmed also by the internal medicine consultation. A cardiologist examination was requested due to hypotension arising during hospitalization: non-critical illness was documented, and a supportive therapy with midodrine was indicated.

With a proper pharmacological treatment, the symptoms decreased. The psychometric scale of evaluation showed a marked decrease in the overall evaluation (BPRS decrease 48%) with an improvement in the mood state (HAM-D decrease 74%) and reduction of anxiety (HAM-A decrease 78%). After 30 days of hospitalization, the patient was discharged from the psychiatric ward with the indication to continue the treatment in the day hospital (DH) of our department. At discharge the therapy comprised valproic acid 400 mg intravenous in addition to 900 mg per day orally, gabapentin 900 mg per day, chlorpromazine 75 mg per day, dothiepin 75 mg per day, and ketazolam 60 mg per day, with specific therapy for hypotension (dihydergot 10 gtt per day), hypothyroidism, and gastroprotection. According to SCID-I for DSM-IV-TR, the diagnosis at discharge was mood disorder due to a medical condition and organic affective disorder according to ICD-9.

For approximately 10 days the patient was seen daily in DH, with intravenous therapy with valproic acid 400 mg. Gabapentin was slightly increased to 1200 mg/day, and oral valproic acid decreased to 300 mg/day and chlorpromazine to 50 mg/day. The patient showed a fair improvement in her global functioning that permitted her to go back to her hometown, improve social relations, and go back to work; she maintained it till February 2016. She started a family psychoeducation aimed at resolving her conflict with her mother and husband, reporting partial benefits. In February 2016, she reported a worsening of her psychopathological state characterized by depressed mood, clinophilia, social isolation, anxious symptoms, and somatizations (muscle tension, tremors, difficulty in swallowing). This relapse led her to quit her job and to several arguments in her family, increasing her distress. She came back to DH, and an oral therapy based on levomepromazine 50 mg/day and chlordesmethyldiazepam 2 mg intravenous was started, in addition to the oral therapy that she reported to have taken regularly in the last months. Only a partial symptomatology stabilization occurred; in May 2016 a further worsening of her symptoms brought her again to hospitalization. She was treated with gabapentin 900 mg per day and intravenous valproic acid 200 mg per day, as a second mood stabilizer. Dothiepin 75 mg/day was continued as antidepressant medication. Clonazepam up to 6 mg/day, in association with delorazepam 4 mg/day and ketazolam 60 mg per day, was introduced to control anxiety symptoms. During hospitalization, blood pressure reported low values (mean value around 90/60 mmHg), and dihydroergotamine mesylate 40 gtt per day in addition to hydrocortisone intravenous 100 mg per day permitted a good control of blood pressure. The patient showed a decrease in anxiety with a reduction of lower limb distress and somatization in general. The patient was discharged after 27 days, and a mood disorder due to a medical condition diagnosis (DSM IV-TR)/organic affective disorder (ICD-9) was confirmed. Patient's mood and anxiety levels reached a normalization that permitted her to go back to her hometown where she was later followed at the local psychiatric

services. A wellness period occurred till November 2016 when she again experienced an increase of the anxiety symptoms with depressed mood and increased concerns on somatic symptoms. In the same period, she divorced her husband, perceived as a huge stressor. During hospitalization fluvoxamine 150 mg per day and mirtazapine 30 mg per day were added to her usual therapy. She underwent additional imaging study with a MRI (Fig. 12.1b) that reported a slight increase of the sulci and gyrus, confirming a minimal diffuse cortical atrophy and minor signal alterations in the subcortical frontal lobe. Neuropsychological tests were carried out a second time and reported a worsening in overall functions with speech, memory, motor proficiency, and frontal proficiency all above the limit. Receiving benefit from the hospitalization, the patient reported a partial remission of her symptoms that permitted, after 14 days, discharge from the psychiatric ward. She was followed daily at the DH, but, after few days of follow-up, the patient reported a further worsening with restlessness, anxiety, somatizations (she described the feeling of "snakes" in her lower limbs and tremors also in the upper limbs), and side effects attributed to the medicine. Due to the impossibility of treating her in a DH setting, she was admitted for the 5th time to the psychiatric ward of our clinic. She was treated with fluvoxamine 150 mg per day, mirtazapine 30 mg/day, and dothiepin 75 mg/day, as she was before admission. Gabapentin 900 mg per day and valproic acid 300 mg per day orally in addition to intravenous valproate 400 mg were continued. Selegiline 5 mg per day was introduced, and chlorpromazine 150 mg/day was started to control involuntary movements. During hospitalization 24 hours of blood pressure monitoring and cardiologic evaluation excluded any pathological reasons responsible for the hypotension. After 30 days of hospitalization, her mood state reached a stable level, with a reduction of the anxiety symptoms, but without reaching a complete normalization. The patient still reported some somatic symptoms (especially a sensation of restlessness in the lower limbs) that she could better control with a reduction of the stressful situations in her daily life. She was followed regularly for 20 days in the DH, and later she went back to her hometown to live with her mother, followed at the local psychiatric services, reporting a temporary stabilization of the symptoms.

Figure 12.3 shows the timeline of patient's history.

12.3 Discussion

The symptoms described in this clinical case report cannot be framed into a unique diagnostic category, due to different psychopathological aspects that need to be underlined. Anxiety symptoms, somatization, and emotion dysregulation are central features in patient's psychopathology, and a link between these can be traced.

As mentioned in the introduction, GAD is a quite common disorder, and referring to Box 12.1, our patient reported feelings of restlessness, muscle tension, sleep disturbance, difficulty in concentrating, and irritability. These physical and psychological symptoms, associated with general worries and concerns perceived most of the day, were present for a long period, without a proper pharmacological treatment

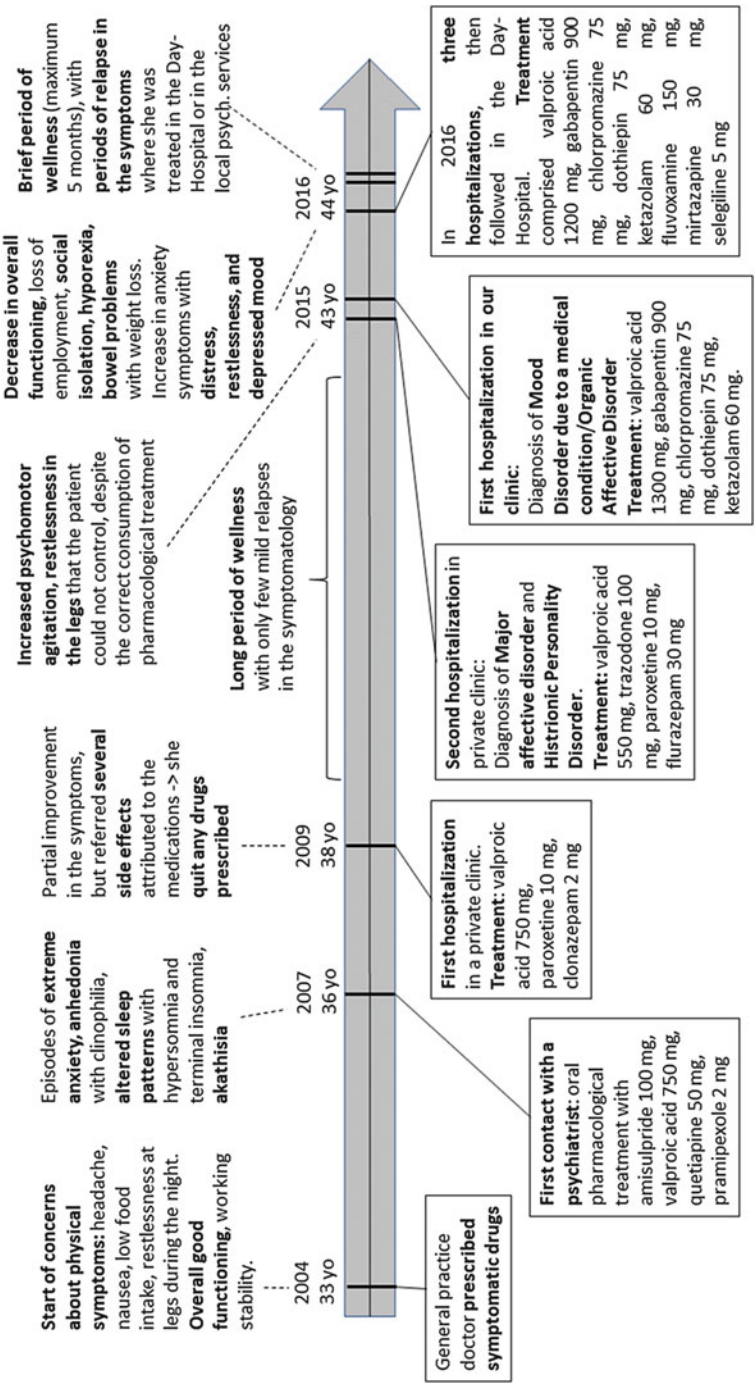

Fig. 12.3 Patient's history timeline

set. Moreover, the symptomatology caused a marked functional deterioration with inability to work and problems with her husband.

If we consider the functional neurological symptom disorder criteria listed in Box 12.2, our patient reported different neurological symptoms, in particular physical complaints in the lower limbs. This concern started with restlessness during the night and turned into involuntary movement in the legs with tremors and shakes also during the day, also depicted during the first neurologist examination she received. During the last hospitalization, the patient also referred sensory alterations, with feelings of "snakes moving" in the lower limbs and tremors also in the arms. No neurological/medical disease could explain the symptoms reported, as indicated by the neurologist's response. Overall, an overlap between a GAD and functional neurological symptom disorder may be underlined. In this respect, tremors and shaking of the limbs in particular can be considered as either linked with anxious burden or secondary to functional aspects.

If we consider the third central feature of patient's psychopathology, emotion dysregulation, a keystone may be found. As noted above, ED is a psychopathological trait associated with different psychiatric disorders and, in particular, with a variety of anxiety disorders [22]. Deficit in emotion regulation may be due to ineffective coping with conditioned fear responses, leading to fear reactions that seem aversive and uncontrollable, leading to a reconditioning in the reactions and to avoidance behaviors that could be chronic. In this respect, when compared with non-anxious controls, individuals with GAD reported poorer understanding of emotions, greater negative reactivity to emotions, and less ability to self-soothe after experiencing negative emotions [23, 24]. Additionally, emotion regulation has long been thought to play a central role in the development of somatoform symptoms. The concept of alexithymia, referring to the difficulty in identifying and describing emotions, can also be introduced in our clinical presentation. Individuals unable to detect, name, and express emotions are more prone to have difficulties using cognitive resources to regulate emotions and, thus, have an increased likelihood of misrepresenting bodily sensations accompanying emotions [25]. In recent years, different studies have shown substantial evidence that somatoform disorders are associated with deficits in the abilities to consciously experience and tolerate emotions, correctly identify emotions, and accurately link emotions to body sensations [18]. In our clinical case, ED could be responsible for the huge distress perceived by the patient, which is then expressed with an increased level of anxiety and somatization, being these the only ways she knows to express emotions, due to her inner inability to control and modulate them.

As mentioned in the introduction, GAD, functional neurological symptom disorder, and ED share alterations in neurological patterns, especially those associated with the limbic system. Imaging studies performed during hospitalization might reveal an organic cause of the symptoms reported. In particular, MRI studies reported a cortical atrophy in the parietal and frontal lobe, while PET studies depicted a globally diffused reduction of the concentration of the tracer. As reported in literature, the frontal lobe and its connectivity with the amygdala are important factors implicated in emotions, social life expression, and behavior regulation. PET

has been widely used in the study of psychiatric disorders, and several alterations have been reported in literature. Our patient showed several depressive features like depressed mood, social isolation, and suicidal ideation. A global dysfunction demonstrated by lower cerebral blood flow and decreased cerebral metabolism are the most common findings in depressed patients [26], and this aspect was found also in ours. Instead, in relation to GAD, lower tracer concentration in the basal ganglia and in the white matter and relatively increased metabolism in the left inferior occipital lobe, right posterior temporal lobe, and right precentral frontal gyrus were reported in literature [27], but not confirmed in our case. Overall, the results of imaging study reported in our clinical case do not address a causality issue between symptoms expressed and the alterations found, but could help to correctly characterize the disorder and make a proper differential diagnosis. Furthermore, in clinical practice, an additional evaluation with functional MRI should be encouraged, due to its importance in depicting altered pattern in brain circuits and its correlation with brain disorders, and may yield therapeutic benefits.

The treatment approach used in this case, yet another time, was not based on a unique diagnosis. Antidepressants have become first-line pharmacological treatments in patients with GAD, based on efficacy and tolerability in different randomized controlled trials. As GAD tends to manifest with a chronic course, long-term treatment is usually required. Relapse prevention studies support the long-term efficacy of a range of pharmacological treatments, including some SSRIs (escitalopram, paroxetine) and SNRIs (duloxetine and venlafaxine) [28]. However, the SSRIs and SNRIs have some efficacy limitations, such as lack of response in many cases, a 2- to 4-week delay before the onset of symptom relief, lack of full remission, and risk of relapse. Evidence from early clinical studies of atypical antipsychotics indicates that they may have a potential role in the treatment of anxiety and GAD. In this respect, low-dose augmentative quetiapine may be a useful treatment option for patients with GAD and partial/no response to SSRIs, as reported in a recent randomized clinical study [29]. Lastly, the antianxiety drug pregabalin provides some benefits in GAD treatment [30].

In relation to functional neurological symptom disorder, to date there are no official guidelines for the treatment. Different therapeutic approaches, including pharmacotherapy (mainly antidepressants), psychological therapies (both cognitive-behavioral and psychodynamic), hypnotherapy, and physical rehabilitation, have been considered helpful in a variable proportion of patients [31]. Transcranial magnetic stimulation has been a subject of recent interest as a potential treatment for functional movement disorders [32].

If we agree with the concept of ED, we must evaluate whether ED is the main psychopathological domain or a common trait in different comorbid psychiatric disorders affecting our patient. The therapeutic target of an altered emotion regulation is still controversial. Different behavior therapies have been proposed to treat ED in different disorders, but no pharmacological treatments have been specifically targeted to control ED itself [18]. In the end, a treatment should be direct to control symptoms, like mood fluctuation, anxiety, and somatization depicted in our clinical case.

According to patient pharmacology history, she was initially treated with a mood stabilizer (valproic acid) and atypical antipsychotics (quetiapine and amisulpride). During the first hospitalization in our department, a second mood stabilizer (gabapentin) was added. She was also treated with antidepressant medication. In particular, she received SSRIs (paroxetine, fluvoxamine), SARI (trazodone), tricyclic antidepressant (dothiepin, amitriptyline), and NaSSA (mirtazapine). All antidepressant compounds were used in association with a mood stabilizer, in order to ameliorate her depressed mood without increasing anxiety symptoms.

Additionally, it is worth noticing the long period of illness after the onset of the symptomatology without a proper pharmacological intervention set, clinically defined as duration of untreated illness (DUI). In this respect, our patient stayed at least 3 years without receiving the appropriate medications. A long DUI seems to be the rule rather than the exception in anxiety disorders, as shown in a clinical study where DUI was approximately 6 years in patients suffering GAD. Moreover, different clinical variables were reported to play a role in determining DUI, which, in turn, has therapeutic and prognostic outcomes [33].

Looking back over the patient's timeline, a progressive worsening of symptomatology and clinical response is clear: at the beginning, she completely recovered after the first hospitalization, and she could go back to her job and reconstitute her social life. After the last committal, however, a subthreshold symptomatology was observed, and two hospitalizations occurred one close to the other. This clinical presentation reflects the course of an organic affective disorder, in which a pharmacological treatment fights against a global worsening in the neuronal pathways. In this respect, as mentioned above, our patient showed, 1 year after the first hospitalization, a marked deterioration in cognitive functions, especially in the frontal ones, as outlined also in MRI and PET studies; the specific cause of this progressive worsening is not known and cannot be determined easily. One possible associated factor might be birth complications, as described, due to the use of the forceps. Literature data are concordant on the association between some perinatal complications and mental illness onset [34]. Our patient suffered from hypothyroidism, which could be associated with altered mood, psychosis, and cognitive deficits [35], but a good control with levothyroxine was always guaranteed and not related to changes in symptomatology. Treatment partial efficacy in controlling symptoms could be another proof that an organic cause could have played an important role in the patient's illness.

According to our clinical interpretation, the patient does not show the ability to adaptively cope with the external world, and any external event is seen as impossible to confront, causing her to express her discomfort with extreme anxiety and with physical symptoms: both can recall GAD and functional neurological symptom disorder. Looking back over the patient's history, she also experienced the inability to deal with emotional distress: her difficulties with her mother and her husband could be seen as secondary to her psychopathology and not vice versa as a possible cause of the condition.

Key Points

- General anxiety disorder (GAD) is a common mental health condition characterized by an excessive and persistent worry about everyday life with no obvious reasons and not restricted to circumstances.
- Patient's concern about physical symptoms is known as somatization that, when associated to a worsening in the global functioning, DSM-5 describes as specific diseases in the diagnostic group of "somatic symptom and related disorders."
- Emotional dysregulation is an emotional response to external stimuli that is poorly modulated that can be characterized by marked and rapid fluctuation of mood and behaviors.
- If a patient comes to your attention with a symptomatology overlapping between anxiety disorders, somatic disorders, and mood disorders, a possible link between these conditions can be pointed out.

Self-Assessment Questionnaire

1. Which of the following sentences about the epidemiology of GAD is true?
   (A) **It is more common in female and in the elderly.**
   (B) It is less common in high-income countries.
   (C) It is associated with smoking.
   (D) It is a rare disorder, with a prevalence $< 1\%$ in the general population.
2. Which of the following diseases is not included in the DSM 5 diagnostic group of "somatic symptom and related disorders"?
   (A) Somatic symptoms disorder
   (B) Illness anxiety disorder
   (C) **Body dysmorphic disorder**
   (D) Functional neurological symptom disorder
3. Which is one of the main brain structures implicated in the regulation of emotional response?
   (A) **The prefrontal cortex**
   (B) The basal nuclei
   (C) The corpus callosum
   (D) The postcentral gyrus
4. Which is the most common alteration in positron emission tomography study associated with patients affected by depression?
   (A) Decreased diffuse captation of the tracer
   (B) Augmented captation of the tracer in the frontal lobe
   (C) **Decreased captation of the tracer in the frontal lobe**
   (D) Decreased captation of the tracer in the limbic system
5. Which could be the best therapeutic approach for this clinical case?
   (A) Antidepressants
   (B) **Antidepressants + mood stabilizers**
   (C) Antipsychotics
   (D) Cognitive behavior therapy

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.
2. Ruscio AM, Hallion LS, Lim CCW, et al. Cross-sectional comparison of the epidemiology of DSM-5 generalized anxiety disorder across the globe. JAMA Psychiat. 2017;74(5):465–75.
3. Weisberg RB. Overview of generalized anxiety disorder: epidemiology, presentation, and course. J Clin Psychiatry. 2009;70(Suppl. 2):4–9.
4. Bandelow B, Boerner JR, Kasper S, Linden M, Wittchen H-U, Möller H-J. The diagnosis and treatment of generalized anxiety disorder. Dtsch Arztebl Int. 2013;110(17):300–9.
5. Zhang X, Norton J, Carrière I, et al. Preliminary evidence for a role of the adrenergic nervous system in generalized anxiety disorder. Sci Rep. 2017;7:42676.
6. Mochcovitch MD, da Rocha Freire RC, Garcia RF, Nardi AE. A systematic review of fMRI studies in generalized anxiety disorder: evaluating its neural and cognitive basis. J Affect Disord. 2014;167:336–42.
7. Delvecchio G, Stanley JA, Altamura AC, Brambilla P. Metabolic alterations in generalized anxiety disorder: a review of proton magnetic resonance spectroscopic studies. Epidemiol Psychiatr Sci. 2017;26(6):587–95.
8. Fricchione G. Clinical practice. Generalized anxiety disorder. N Engl J Med. 2004;351 (7):675–82.
9. Vargas-Prada S, Coggon D, Ntani G, et al. Descriptive epidemiology of somatizing tendency: findings from the CUPID study. PLoS One. 2016;11(4):e0153748.
10. Hollifield MA. Somatoform disorders. In: Sadock BJ, Sadock VA, editors. Kaplan and Sadock's comprehensive textbook of psychiatry. 8th ed. New York: Lippincott Williams & Wilkins; 2005. p. 1808.
11. Haftgoli N, Favrat B, Verdon F, et al. Patients presenting with somatic complaints in general practice: depression, anxiety and somatoform disorders are frequent and associated with psychosocial stressors. BMC Fam Pract. 2010;11(1):67.
12. Atmaca M, Sirlier B, Yildirim H, Kayali A. Hippocampus and amygdalar volumes in patients with somatization disorder. Prog Neuro-Psychopharmacol Biol Psychiatry. 2011;35 (7):1699–703.
13. van der Kruijs SJ, Bodde NM, Vaessen MJ, et al. Functional connectivity of dissociation in patients with psychogenic non-epileptic seizures. J Neurol Neurosurg Psychiatry. 2012;83 (3):239–47.
14. Ejareh Dar M, Kanaan RA. Uncovering the etiology of conversion disorder: insights from functional neuroimaging. Neuropsychiatr Dis Treat. 2016;12:143–53.
15. Sheppes G, Suri G, Gross JJ. Emotion regulation and psychopathology. Annu Rev Clin Psychol. 2015;11(1):379–405.
16. D'Agostino A, Covanti S, Rossi Monti M, Starcevic V. Reconsidering emotion dysregulation. Psychiatry Q. 2017;88(4):807–25.
17. Kring S. Emotion regulation and psychopathology: a transdiagnostic approach to etiology and treatment. New York: Guilford Press; 2010.
18. Berking M, Wupperman P. Emotion regulation and mental health: recent findings, current challenges, and future directions. Curr Opin Psychiatry. 2012;25(2):128–34.
19. Hilt L, Hanson J, Pollac S. Emotion dysregulation. In: Brown B, Prinstein M, editors. Encyclopedia of adolescence. Wyman, MA: Elsevier; 2011. p. 160–9.
20. Davidson RJ. Anxiety and affective style: role of prefrontal cortex and amygdala. Biol Psychiatry. 2002;51(1):68–80.
21. Farb NAS, Anderson AK, Segal ZV. The mindful brain and emotion regulation in mood disorders. Can J Psychiatr. 2012;57(2):70–7.
22. Cisler JM, Olatunji BO, Feldner MT, Forsyth JP. Emotion regulation and the anxiety disorders: an integrative review. J Psychopathol Behav Assess. 2010;32(1):68–82.

23. Tull MT, Jakupcak M, Roemer L. Emotion suppression: a preliminary experimental investigation of its immediate effects and role in subsequent reactivity to novel stimuli. Cogn Behav Ther. 2010;39(2):114–25.
24. Novick-Kline P, Turk CL, Mennin DS, Hoyt EA, Gallagher CL. Level of emotional awareness as a differentiating variable between individuals with and without generalized anxiety disorder. J Anxiety Disord. 2005;19(5):557–72.
25. De Gucht V, Heiser W. Alexithymia and somatization: quantitative review of the literature. J Psychosom Res. 2003;54(5):425–34.
26. Drevets WC, Price JL, Furey ML. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. Brain Struct Funct. 2008;213 (1-2):93–118.
27. Newberg AB, Moss AS, Monti DA, Alavi A. Positron emission tomography in psychiatric disorders. Ann N Y Acad Sci. 2011;1228(1):E13–25.
28. Baldwin DS, Hou R, Gordon R, Huneke NTM, Garner M. Pharmacotherapy in generalized anxiety disorder: novel experimental medicine models and emerging drug targets. CNS Drugs. 2017;31(4):307–17.
29. Altamura AC, Serati M, Buoli M, Dell'Osso B. Augmentative quetiapine in partial/nonresponders with generalized anxiety disorder: a randomized, placebo-controlled study. Int Clin Psychopharmacol. 2011;26(4):201–5.
30. Katzman MA. Current considerations in the treatment of generalized anxiety disorder. CNS Drugs. 2009;23(2):103–20.
31. Demartini B, Batla A, Petrochilos P, Fisher L, Edwards MJ, Joyce E. Multidisciplinary treatment for functional neurological symptoms: a prospective study. J Neurol. 2014;261 (12):2370–7.
32. Lehn A, Gelauff J, Hoeritzauer I, et al. Functional neurological disorders: mechanisms and treatment. J Neurol. 2016;263(3):611–20.
33. Benatti B, Camuri G, Dell'Osso B, et al. Which factors influence onset and latency to treatment in generalized anxiety disorder, panic disorder, and obsessive–compulsive disorder? Int Clin Psychopharmacol. 2016;31(6):347–52.
34. Mansur RB, Cunha GR, Asevedo E, et al. Perinatal complications, lipid peroxidation, and mental health problems in a large community pediatric sample. Eur Child Adolesc Psychiatry. 2017;26(5):521–9.
35. Testa A, Giannuzzi R, Daini S, Bernardini L, Petrongolo L, Gentiloni SN. Psychiatric emergencies (part III): psychiatric symptoms resulting from organic diseases. Eur Rev Med Pharmacol Sci. 2013;17(Suppl 1):86–99.