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Psychiatric emergencies (part III): psychiatric symptoms resulting from organic diseases

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Abstract. – An exhaustive review on the *organic illnesses* presenting with psychiatric manifestations, properly defined *pseudopsychiatric emergencies*, is presented. A systematic classification of the numerous organic causes of *psychiatric disorders*, based on authors' experience and literature revision, is carefully analysed, and their suitable diagnostic management in emergency setting is proposed. Moreover, the role of bedside ultrasonography in Emergency Department is emphasized.

The underlying pathogenetic mechanisms are separately discussed. A particular significance is given to "*neuropsychological studies*", displaying the complex connection between the central nervous system and the endocrine system. The role of immune system in influencing the central nervous system, explaining the model of "*sickness behaviour*" in inflammatory disease, is also described, according to recent reports of "*psychoneuroimmunology*". Moreover, the immune-mediated mechanism explaining how neoplasm can influence brain function in the "*paraneoplastic syndromes*" is shown.

In order to facilitate the teaching method, organic illnesses presenting with *acute psychic manifestations* or mimicking specific psychiatric disorders are subdivided into three groups: (1) *Endocrine* and *metabolic disorders* and *deficiency states*; (2) Internal diseases; (3) Neurologic disorders.

Key Words:
Psychiatric emergencies, Psychiatric disorders, Pseudopsychiatric emergencies, Bedside ultrasonography, Emergency ultrasonography.

Abbreviations

ABG = arterial blood gas
CABG = coronary artery bypass graft
CCA = common carotid artery
CNS = central nervous system
COPD = chronic obstructive pulmonary disease
CSF = cerebro-spinal fluid
CT = computed tomography
ECG = electrocardiogram
ED = emergency department
EEG = electroencephalogram
HIV/AIDS = human immunodeficiency virus/acquired immune-deficiency syndrome
IBD = inflammatory bowel disease
ICD = implantable cardioverter defibrillator
ICU = intensive care unit
MR = magnetic resonance
NMDAr = N-methyl-D-aspartate receptor
OSAS = obstructive sleep apnea syndrome
TIA = transient ischemic attack
US = ultrasonography

Introduction

Background and General Approach

The conditions in which *medical disorders* produce *acute psychic manifestations* or mimic specific *psychiatric disorders* constitute the so called *pseudopsychiatric emergencies*, which represent up to 10% of all psychiatric disorders[1]. The management of patients displaying psychiatric disorders in the ED disconcerts the staff because of the irrational, unpredictable and often violent behaviour of these patients. On the other hand, a correct and prompt diagnosis is crucial in order to decide the right management and obtain hence a good prognosis.

Medical Diseases Mimicking Psychiatric Disorders

An exhaustive recognition of the organic diseases that can present as psychiatric disorder is afterwards presented, assembling 3 main groups: (1) *Endocrine and metabolic disorders and deficiency states* (Table I); (2) *Internal diseases* (Table II); (3) *Neurologic disorders* (Table III).

Endocrine and Metabolic Disorders and Deficiency States

Endocrine Diseases

The *hypothalamic diseases* cause most frequently bulimia or anorexia, hypersomnia, im-

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Table I. *Endocrine and metabolic disorders* and *deficiency states* potentially producing acute *psychic symptoms* or mimicking *psychiatric disorders* (*pseudopsychiatric emergencies*).

	Psychosis	Depression	Mania	Anxiety	Behavioural and vegetative symptoms	Cognitive deficit	Consciousness impairment
Endocrine disorders							
Hypopituitarism/ hypothalamus disease	+			+	+	+	+
Hyperprolactinemia		+		+	+	+	
Hypothyroidism	+	+	+	+	+	+	+
Hashimoto encephalopathy	+	+	+	+	+	+	
Hyperthyroidism	+	+	+	+	+		
Addison's disease	+	+				+	
Cushing's disease	+	+		+	+		
Pheochromocytoma					+		
Premenstrual syndrome	+	+			+	+	
Postpartum psychosis	+	+		+	+		
Menopause		+					
Male hypogonadism		+			+	+	
Fluids and electrolitic disorders							
Dehydration and heatstroke	+				+	+	+
Hyponatriemia	+			+	+	+	+
Hypernatriemia					+	+	+
Hypocalcemia	+			+			
Hypercalcemia	+	+			+		+
Hypomagnesiemia		+			+	+	+
Metabolic disorders							
Hypoglycemia	+			+	+	+	+
Hyperglycemia		+		+	+	+	+
Inborn errors of metabolism	+				+	+	+
Deficiency states							
Vitamin B2	+	+	+	+			
Vitamin B6		+					
Vitamin B12 and folate	+	+	+	+			
Vitamin PP	+	+		+	+	+	+
Vitamin D	+	+		+			
Wernicke-Korsakoff syndrome	+	+	+	+	+	+	+
Zinc		+					

potency, and attacks of anxiety, while the main psychiatric symptoms of *hypopituitarism* are a combination of dementia and delirium[2]. Relationship between *hyperprolactinemia* and psychosis are complex and mutual. Hyperprolactinemia is treated with dopamine agonists, which may cause psychotic symptoms as side effect, and psychosis is treated with dopamine-receptor blockers that may result in symptomatic hyperprolactinemia. Effects of hyperprolactinemia on mood and behaviour include depression, eating disorders and anxiety. Other psychiatric symptoms may arise from the mass effect of a *pituitary adenoma*, with visual or olfactory hallucinations, episodes of "losing time" and apathy[3].

Hashimoto's thyroiditis is the most common cause of *hypothyroidism* in adult, easily detectable yet in ED by bedside US (Figure 1), other than by TSH and FT4 samples. High impairment of the recent memory, lack of initiative, diminished learning ability and speech deficit are the characteristic mental manifestations of hypothyroidism. Letargia, confusional state and coma, especially if added to precipitating factors, can then develop (*myxedema coma*)[4]. Dementia should be considered in differential diagnosis in elderly patients, complaining psychiatric symptoms like severe anxiety manifestations, depressive or paranoic disorders, acute psychosis and marked agitation ("*myxedema madness*")[5]. Recently, "*Hashimoto's encephalopathy*" has been described, referable to

Table II. Main *internal diseases* more commonly causing acute *psychic symptoms* or mimicking *psychiatric disorders* (*pseudopsychiatric emergencies*).

	Psychosis	Depression	Mania	Anxiety	Behavioural and vegetative symptoms	Cognitive deficit	Consciousness impairment
Respiratory diseases							
Hypoxiemia	+	+	+	+		+	
Hypercarbia	+				+	+	+
Pulmonary oedema	+			+			
Pulmonary embolism				+			
Lung transplantation		+		+			
OSAS		+	+		+	+	
COPD		+		+			
Asthma		+		+			
High-altitude illness	+			+	+	+	
Heart diseases							
Congestive heart failure/hypotension	+			+		+	
Coronary artery disease		+		+			
CABG	+	+					
Mitral valve prolapse				+			
Cardiac dysrhythmias				+			
ICD			+		+		
Heart valve operation	+						
Heart transplantation		+		+			
Haematologic diseases							
Anemia	+			+	+	+	+
Polycythemia	+	+		+	+	+	+
Leukaemia	+	+		+	+	+	+
Thrombocytopenia	+						
Sickle cell disease	+	+		+	+	+	+
Hypereosinophilia			+				
Gastroenteric diseases							
Celiac disease	+	+					
Inflammatory bowel disease		+		+	+		
Whipple's disease	+	+		+	+	+	
Hepatic failure							
Hepatic encephalopathy	+	+	+	+	+	+	+
Renal failure							
Uremia	+	+			+	+	+
Acute urinary retenction				+	+	+	+
Dermatologic diseases							
Psoriasis		+			+		
Acne vulgaris		+		+	+		

Table coninued

an immuno-mediated pathogenesis, attributable to the special neuropsychiatric picture observed in any age patients with Hashimoto's thyroiditis, and represented by intellectual deterioration, seizures, agitation, mood disorders and hallucinations, regardless of the thyroid function[6]. *Graves disease* is the most serious and typical form of *hyperthyroidism*, sometimes presenting as "*thyroid storm*", even due to the attendant typical facies, characterized by exophthalmus[4,7]. Bedside US can detect an enlarged and dyshomogeneous thyroid gland displaying a diffuse hypervascularity on color-Doppler imaging (*"thyroid inferno"*)[8]. Psychiatric manifestations range from a simple emotive lability, to an exasperated anxious symptomatology; in this condition could emerge more severe disorders as bipolar syndrome, paranoid reactions and a clear psychosis[7]. When psychiatric symptoms still persist after the hormone normalization, an immune-mediated cause is supposed.

Table II *(Continued).* Main *internal diseases* more commonly causing acute *psychic symptoms* or mimicking *psychiatric disorders* (*pseudopsychiatric emergencies*).

	Psychosis	Depression	Mania	Anxiety	Behavioural and vegetative symptoms	Cognitive deficit	Consciousness impairment
Inflammatory and infectious diseases							
"Sickness behaviour"		+			+		
Sistemic lupus erythematosus	+	+	+	+	+	+	
Antiphospholipid syndrome	+	+	+	+	+	+	
Sjögren's syndrome	+					+	
Behçet's disease						+	
Reumathoid arthritis		+			+		
Temporal (giant cell) arteritis	+	+	+	+		+	
Rheumatic fever (PANDAS)			+		+		
Sarcoidosis	+					+	
Fever and sepsis	+			+	+	+	+
Brucellosis	+	+	+	+	+	+	+
Malaria	+	+	+	+	+	+	+
Enteric (typhoid) fever	+	+	+	+	+		+
Neuroborreliosis (Lyme disease)	+	+	+	+	+	+	+
HIV/AIDS	+	+	+	+	+	+	
Mononucleosis		+		+	+		
Neoplasms (paraneoplastic syndrome)							
Neoplastic disease		+	+	+	+	+	
Limbic encephalitis					+	+	
Frontal disequilibrium					+	+	
Metal poisoning							
Lead					+		
Mercury, aluminium, manganese, copper						+	

In *pheochromocytoma* the epinephrine hypersecretion can mimic a panic attack. Elevated plasma and urinary catecholamine, and related metabolites, can be assayed during or immediately after the clinical manifestation. The identification of an adrenal mass by bedside US may contribute to confirm the diagnosis.

Psychiatric disorders in *Addison's disease* are present in the longstanding form and include anorexia, depression and psychosis. The diagnosis is simplified by the presence of hyperpigmentation, and by routine laboratory tests (reduced sodium-potassium ratio, lymphocytosis and eosinophilia), and confirmed by low cortisol and high ACTH levels in the primary adrenal failure. Psychiatric manifestations also appear in up to 50% in *Cushing's syndrome,* with prevalence of depressive symptoms, which may induce to suicidal ideation, rarely to anxious disorders, maniac forms and psychotic manifestations[9].

The association between *gender-related endocrinological dysfunctions* and neuropsychiatric disorders was established long ago, with solid evidence[10]. *Premenstrual syndrome* affects about 30% of premenopausal women, with dysphoric disorders that cause severe dysfunction in social or occupational environments[11]. Onset or exacerbation of anxious or depressive disorders, bipolar disorders and psychosis frequently occur in *peripartum period*, heavily contributing to maternal mortality and neonate carelessness[12]. Recent studies indicate that the likelihood of depressed mood in the *menopause* is approximately 30% to three times greater compared with that during premenopause[13]. Similarly, *hypogonadism* in man can cause depressive disorders beside reduced libido, erectile dysfunction, reduced muscle mass and strength, increased adiposity, osteoporosis, low bone mass and fatigue[14].

Table III. *Neurologic disorders* potentially producing acute *psychic symptoms* or mimicking *psychiatric disorders* (*pseudopsychiatric emergencies*).

	Psychosis	Depression	Mania	Anxiety	Behavioural and vegetative symptoms	Cognitive deficit	Consciousness impairment
Head trauma							
Post-commotive state				+	+		
Epi- and subdural haematoma	+	+	+	+	+	+	+
Cerebral contusion and haematoma	+	+	+	+	+	+	+
Diffuse brain lesion	+	+	+	+	+	+	+
Post-traumatic brain injuries	+	+	+	+	+	+	
Brain neoplasms							
Frontal lobe syndrome	+	+	+	+	+	+	+
Radiotherapy and chemotherapy	+	+	+	+	+	+	+
Cerebral vascular accidents							
TIA		+		+			
Stroke	+	+	+	+	+	+	+
Chronic cerebral vascular disease	+	+	+	+	+	+	+
Brain inflammatory diseases							
Autoimmune limbic encephalitis					+	+	
Anti-NMDAR encephalitis	+	+	+		+		+
Brain infectious diseases							
Meningitis and encephalitis	+	+	+	+	+	+	+
Neurosyphilis	+	+	+	+	+	+	+
Brain degenerative diseases							
Alzheimer's disease	+	+	+	+	+	+	+
Vascular dementia	+	+	+	+	+	+	+
Huntington's disease	+	+	+	+	+	+	+
Parkinson's disease	+	+	+	+	+	+	+
Multiple sclerosis	+	+	+	+	+	+	+
Wilson's disease	+	+	+	+	+	+	+
Toxic encephalopathy							
Industrial toxins and pesticides	+				+	+	
Epilepsy							
Focal epilepsy (temporal/frontal lobe)	+	+	+	+	+	+	
Non-convulsivant status of epilepsy	+	+	+	+	+	+	+
Hydrocephalus							
Normal-pressure hydrocephalus	+	+	+	+	+	+	+

Electrolytes Disorders

Mood and various cognitive functions, including vigilance, reaction times, attention, memory and reasoning may be impaired by *dehydration*, especially in elderly and childhood, and after prolonged exercise or high temperature exposure[15]. Multisystem tissue damage involved in *heatstroke*, with body temperature usually >40.5°C and hypertransaminasemia, results in severe neuropsychiatric dysfunction, with bizarre behaviour, hallucinations, delirium and coma.

Electrolytes disturbances are frequently depicted in ED, brain being the principal organ affected, with a variety of reversible neuropsychiatric manifestations. The clinical expression of *hyponatremia* are strictly bound to its entity (<125 mmol/l) and rapidity of its onset. In acute forms the hyperexcitability till seizures is frequent, while in chronic hyponatremia sopor and confusion up to coma can be observed. The neuropsychiatric complications associated with hyponatremia are attributable to cerebral oedema and increased intracranial pressure. Comorbidity frequently occurs (i.e. heart failure) and drug administration should be carefully investigated[16]. *Hypernatremia* appears with abnormal cognitive status, impaired neuromuscular function and potential risk of haemorrhagic complications, up to coma or death in late stages[17].

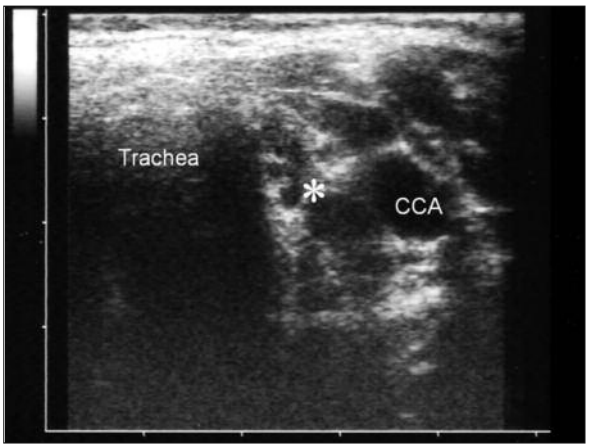

Figure 1. Common sonographic picture in patient suffering for severe hypothyroidism: a case of chronic autoimmune thyroiditis (Hashimoto's) in a 65 year old woman. Thyroid left lobe in a transverse scan (*marked by an asterisk**) seems atrophic, hypoechoic and with inhomogeneous echostructure with wavy borders.

Parathyroid diseases often present with psychiatric symptoms, and can be easily recognized through determinations of low calcium levels. The link between anxiety disorders and *hypocalcemia* is mutual: a panic attack could manifest with tetany by hyperventilation, and hypocalcemia could trigger a panic attack. Medical history can reveal a renal failure or a past thyroidectomy, while electrocardiogram (ECG) shows low and large QRS complex and long QT duration. Moreover, arrhythmia, paresthesia, laryngospasm, muscle cramps and tetany (*obstetrician's hand*) can appear. The increased central neuro-excitability produces instead irritability and seizures, but anxiety is the predominant symptom in 20% of patients[4]. Medical history can confirm the clinical suspect also in *hypercalcemia*, while ECG shows high and short QRS, short QT. Bedside neck US can rule out the diagnosis of a parathyroid adenoma in ED yet, with high diagnostic accuracy. The psychiatric disorders rarely are absent in patients with severe hypercalcemia (>15 mg/dl), and intensify with old age. The more frequent are anorexia, depression, acute psychosis, confusion and coma[4].

Hypomagnesemia results in a profound effect on neural excitability, with symptomatology previously described in medical literature as latent tetany, hyperventilation syndrome, spasmophilia or chronic fatigue syndrome. Coexistent irritabilitity, depression, confusion and disorientation should suggest this disorder, especially if associated to neurologic, cardiac and gastro-intestinal symptoms, and to an inexplicable hypokalemia and hypocalcemia[18].

Metabolic Disorders

Reactive *hypoglycemia* is often considered the cause of anxiety symptoms in diabetic patients. Actually, hypoglycemia presents with symptoms related to autonomic activation, involving the psychic field with behavioural disorders and anxiety (adrenergic symptoms), and related to neuronal suffering (neuro-glycopenic symptoms), with predominant implication of cognitive (speech difficulty), sensorial (visual disorders, dizziness) and neuromuscular (fatigue) sphere. A normal fingerstick blood glucose analysis can easily exclude or confirm this diagnosis[19]. *Hyperglycemia* represents an emergency with poor prognosis, associated to metabolic acidosis, severe dehydration and electrolytes disorders. The patient can develop a confusional state, irritability or lethargy. A major depressive disorder is seen in about 25% of cases, with worsening of the psychiatric disorder if not reached the glycemic control[20].

Inborn metabolism errors can appear with a confusional state or an acute psychotic episode, but generally suspected by associated systemic dysfunctions and/or for the family history. More common enzymatic deficits are *urea cycle* dysfunctions and *porphyria*. Psychiatric disorders with a chronic progress as hallucination occur in *Wilson disease* (see below), *adrenoleukodistrophy* and some *lysosome diseases*[21].

Deficiency States

Nutritional deficiency leading to cachexia, dehydration, electrolytes impairment and multivitaminic deficiency (*ascorbic acid, riboflavin, pyridoxin, cobalamin, folate*), are frequently associated to depression, mania and psychosis[22]. *Hyperhomocysteinaemia* has been suggested as a cause of Alzheimer's disease. Low levels of *vitamin D* have been associated with exacerbation of anxiety, depression, psychosis[23]. *Wernicke-Korsakoff syndrome* is preventable, life-threatening neuropsychiatric syndrome resulting from *thiamine* deficiency. Neurological symptoms (ataxia, ophthalmoplegia and nystagmus) are associated to various cognitive and psychiatric disorders as amnesia, confabulation and hallucinations, at times showing more complex manifestations as bipolar disorder, somatoform disorder and paranoid schizophrenia. Brain MR imaging shows classic thalamic injury. *Nicotinamide* deficiency may result in a rare condition (pellagra en-

cephalopathy), which often has a similar clinical presentation to Wernicke-Korsakoff syndrome[24], while *zinc* deficiency is related to depression[25].

Internistic Diseases

Respiratory Diseases

Psychic symptoms are common in respiratory failure, referable to *hypoxemia* and *hypercarbia*. *Hypoxemia* produces irritability and mood disturbances, and *hypercarbia* causes mainly cognitive disorders, mild personality disorders, confusion, sleepiness, and narcosis. *Acidosis* contributes to irritability and sleep disorders.

Pulmonary edema and *pulmonary embolism* can present with choking sensation associated to anxiety and agitation, fear, sometimes sensation of forthcoming death. Respiratory history and physical examination, pulse oxymetry, chest X-ray, ABG analysis and routine laboratory tests help in diagnosis. Bedside US can confirm a normal "dry lung" in pulmonary embolism (Figure 2A), while an interstitial syndrome, characterized by diffuse B lines pattern, can depict a pulmonary edema (Figure 2B). Delirium is common in *pneumonia*, but it disappears after effective antibiotic treatment. Rates of major depression in *lung transplantation recipients* is 30%, panic disorder 18%, post-traumatic stress disorder 15%, generalized anxiety disorder 4%[26]. *OSAS* is related to sleep disorders, fatigue, headache, cognitive impairment, irritability and mood disturbance[27]. Approximately one third of patients with *COPD* meets the criteria for anxiety disorders, and a quarter shows depression, systemic inflammation being implicated in their pathogenesis, other than corticosteroids[28]. An increased prevalence of depression, anger, anxiety disorders, particularly panic attacks, is also reported in patients with *asthma*, easily identified by thoracic objective alteration and pulse oximetry[29]. Hypoxia is the primary cause of *high-altitude illness*, but other stressors, such as cold and exertion, contribute to disease development. Symptoms of high-altitude disorders usually occur over 2000 meters, and typically in 1 of 3 forms: acute mountain sickness, high-altitude cerebral oedema and high-altitude pulmonary oedema[30].

Heart Diseases

Depression and *cardiac disorders* present a major comorbidity, and their interrelations may be analysed within a biopsychosocial model of disease. Abnormalities of mental function are common problems in patients with *congestive heart failure*. Cardiac output and cerebral blood flow are preserved due to compensatory mechanisms in mild heart failure but can be severely compromised in advanced failure. Drugs used to treat heart failure, especially digitalis, can produce a wide variety of mental aberrations including delirium, while diuretics and vasodilators can produce electrolyte abnormalities and *hypotension*[31]. The relationship between depression and *coronary heart disease* is well-established, but causal mechanisms are poorly understood[32]. *Mitral valve prolapse* can be associated with palpitations and induce anxiety. Similar-

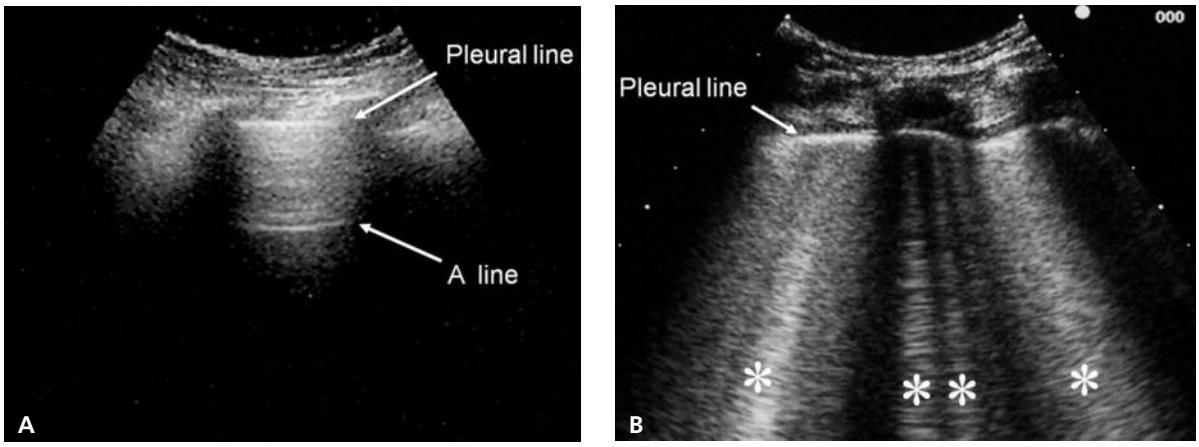

Figure 2. ***A,*** The normal sonographic appearance of the lung on longitudinal scan is shown. Only an A line pattern appears. The A lines are horizontal artifacts that appear at regular intervals, reproducing the distance of the transducer to the pleural line, and fading deeply. ***B,*** US pattern displaying well distinct multiple B lines (*ring down artifacts arising from the pleural line*), defining the interstitial syndrome in pulmonary edema, is shown. B lines (*asterisks*) are roughly vertical and well defined and are spread to the edge of the screen without fading, erasing the A lines and moving synchronically with the lung sliding.

ly, *cardiac arrhythmias* can produce palpitations, discomfort, dizziness and intense apprehension mimicking a panic disorder. Fortunately, the presence of arrhythmias can be promptly confirmed by physical examination and characterized on ECG. A significant proportion (about 20%) of *ICD* patients experiences psychological symptoms including anxiety, depression or both, a rate similar to that in other cardiac populations[33]. Severe psychotic symptoms are reported in 2% of patients undergoing *CABG* and *heart valve operation*, independently associated with a prolonged length of stay on the ICU[34]. Finally, psychiatric disorders are common in *heart transplanted patients*, major depression having highest prevalence (26%). The occurrence of transplant-related post-traumatic stress disorder (14%), panic disorder (8%) and generalized anxiety disorder (3%) are also reported[26].

Haematologic Diseases

Anemia, polycythemia, leukaemia and *thrombocytosis*, by direct damage, ischemic or immuno-mediated mechanism, or indirect drug and/or radiotherapy effect, can provide various pseudopsychiatric pictures[35]. *Thrombocytopenia* is reported associated with neuroleptic malignant syndrome[36]. *Sickle cell disease* conveys a high risk of anxiety and depression, due to chronic anemia, hypoxiemia, cerebrovascular ischemia and stroke, lifelong medical management constituting an additional risk[37]. *Churg-Strauss syndrome* causes cerebral infarction or haemorrhage, and psychiatric symptoms, prevalently delirium, may occur although rarely. Diagnosis should be considered in patients with late onset asthma, *hypereosinophilia* (>1000/mm^3), mononeuritis multiplex, purpura, cardiomyopathy and pulmonary infiltrates[38].

Gastroenteric Diseases

In *celiac disease* a higher prevalence of depressive disorders and schizophrenia was found. Sleep disorders, anxiety and depression are more common in patients with *IBD*[39]. Neuropsychiatric disorders may precede the diagnosis of *Crohn's disease*, including peripheral neuropathy, myopathies, pseudotumor cerebri, papilloedema and psychiatric disorders (anxiety, phobias, depression). Hypercoagulability constitutes one of the pathogenic mechanisms, but alteration of humoral and cellular immunity can explain the neuropsychiatric manifestations[40]. *Whipple's disease,* a multisystemic chronic granulomatous disease caused by infection with *Tropheryma whipplei*, can appear as a primary neuropsychiatric disorder, including cognitive changes and psychiatric findings (depression, anxiety, psychosis, personality change). The brain CT and MR imaging are often normal, but may show cortical/subcortical atrophy, hydrocephalus, focal or intracerebral mass lesions[41].

Hepatic Failure

Liver encephalopathy is characterized by a neuropsychiatric syndrome with a seesaw course, as consequence of a severe impairment of the hepatocellular function and/or of a portal-systemic shunt. The patient can present at the onset as euphoric, anxious, irritable and aggressive; then he could be apathetic, sleepy and disorientated; finally confusion, stupor and coma develop. The diagnosis is based on clinical features and laboratory tests (ammonia, glycemia, sodium, uremia, liver enzymes, alcohol, ABG analysis): the hyperammonia is not proportional to the neuro-psychic impairment[42].

Renal Failure

In *acute renal failure* the onset symptom could be only agitation or confusion, often preceded by sleep disorders, easily diagnosed by routine laboratory tests. Bedside US by chest and abdominal approach allows to rule out pre- and post-renal causes. Normocytic anemia and hypocalcemia are also depicted in *chronic renal failure*, although well tolerated[43]. *Acute urinary retention*, often without any complaining of discomfort, can manifest with acute mental status changes in the elderly patient, as agitation, confusional state or delirium. If physical examination fails in detecting a bladder globe, diagnosis may be easily confirmed by bedside US (Figure 3). A possible pathogenetic explanation for this "*cystocerebral syndrome*" is the increased adrenergic tension in the CNS, when micturition cannot occur at the usual threshold[44].

Dermatologic Diseases

There is an association between *psoriasis* and depression, as well as substance abuse. Elevation of C-reactive protein, homocysteine and inflammatory cytokines may contribute to the overall morbidity and mortality in these patients[45].

Inflammatory and Infectious Diseases

The immune system can influence the CNS by cytokines, produced by activated immune cells. *Sickness behaviour* is a behavioural complex induced by infectious and immune disease, and mediated by pro-inflammatory cytokines. It is an

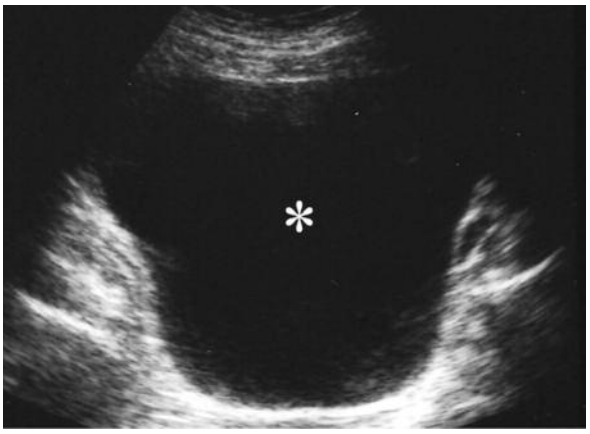

Figure 3. Bladder globe, easily and rapidly detectable by ultrasound (*), example of post-renal acute failure (*obstructive*), more frequent and responsible of behavioural change in elderly, often associated with bilateral hydronephrosis and signs of urosepsis.

adaptive response that enhances recovery by conserving energy to combat acute inflammation[46]. There are considerable phenomenological similarities between sickness behaviour and *depression*, for example, behavioural inhibition, anorexia, adipsy, increased sleepiness, melancholia (anhedonia), anxiety, and somatic symptoms (fatigue, hyperalgesia, malaise). Recently, depression and sickness behaviour have been proposed as Janus-faced responses to shared inflammatory pathways[47].

Several neuropsychiatric pictures are related to *systemic lupus erythematosus*, without reliable imaging or laboratory criteria: cognitive deficit, anxiety, mood disorders, confusion, delirium, and psychosis. Memory alterations, cognitive impairment, mood disorders, and psychosis may precede *primary antiphospholipid syndrome* diagnosis. Similarly, *Sjögren's syndrome* and *Behçet's disease* may have prominent neuropsychiatric symptoms: cognitive dysfunction, peripheral neuropathy, stroke- or multiple sclerosis-like symptoms and personality changes are variously described[48]. Depressive symptoms are frequently associated with *rheumatoid arthritis*[49], and psychotic features and affective symptoms are described in *temporal arteritis*[50]. In *rheumatic fever*, anti-streptococcal antibodies cross-react with heart, joints, skin, and other sites, inducing an inflammatory multisystemic disease. Brain tissue-specific antibodies have been demonstrated in a subset of children with *Sydenham's chorea*, who manifest obsessive-compulsive symptoms. The *PANDAS* defines a homogenous subgroup of children with obsessive-compulsive disorder and/or tic disorders, occurring as a result of post-streptococcal autoimmunity in a manner similar to that of Sydenham's chorea[51]. In *neurosarcoidosis* acute onset of psychosis and dementia may occur. Usually, abnormal MR enhancement are present, while communicating hydrocephalus can arise from meningeal arachnoid granulation involvement[52].

Fever and *septicaemia* can present with psychiatric symptoms (delirious fever), as can chronic *brucellosis*. *Neurobrucellosis* is a rare form of systemic brucellosis, which may manifest as stroke, encephalitis, meningitis, or psychiatric disorders. Brain MR imaging and brucella antigen agglutination test allows correct diagnosis[53]. *Cerebral malaria* is one of the most serious complications of *Plasmodium falciparum* infection. Behaviour and attention disorders, frontal syndrome have been described either as early manifestation or part of post malaria neurological syndrome[54]. Mania and a major depressive and psychotic episodes may occur with mefloquine antimalarial prophylaxis. Psychiatric morbidity can affect about 20% of patients suffering *enteric (typhoid) fever*, appearing with delirium (73%), generalized anxiety disorder (4%), depressive episode (4%), schizophrenia like disorder (4%) and monosymptomatic neuropychiatric manifestations such as apathy, hallucination, confusion and coma. These neuro-psychiatric complications of typhoid fever could be attributed to direct or immune-mediated *Salmonella typhi* bacterial endotoxins or provoked by poor nutrition[55]. The neuropsychiatric manifestations of *neuroborreliosis (Lyme disease)* are so numerous that Borrelia is also called the "new great imitator". Lyme serology must be assessed in case of unexplained neurological or psychiatric disorder, and CSF assessment with intrathecal anti-Borrelia antibody index will prove the diagnosis[56]. *HIV/AIDS*-associated neuropsychiatric syndromes can be classified as primary HIV disease, secondary or opportunistic disease, and treatment-related disease. Anxiety disorders are elevated among HIV+ populations, and post-traumatic stress disorder is commonly reported to develop *in response* to HIV diagnosis. Nearly 25% HIV+ men experience major depression, rates of depressive disorders reaching 65% as a function of disease stage[57]. *Bipolar disorder* and *secondary mania* are also reported among HIV/AIDS patients. Finally, *psychotic symptoms,* with auditory, visual and olfactory hallucinations, may occur in HIV population[58].

Anecdotal reports suggest that chronic fatigue, anxiety and depressive disorders may be precipitated by infectious *mononucleosis*[59].

Neoplasia

Cerebral *paraneoplastic syndrome* was thought to result from neuronal degeneration, viral infection, or immunological alteration, the latter appearing as the main causative mechanism. The prevalence of paraneoplastic syndromes depends on the type of cancer, and it ranges from below 1% in breast and ovarian cancers, to 3–5% in small cell lung cancer, and 20% in thymomas. Antibodies associated with paraneoplastic disorders that often include neuropsychiatric manifestations can be subcategorized on the basis of the cellular locations of the antigens they recognize. The pathogenesis of antibodies directed against *intracellular neuronal antigens* is thought to be mediated by cytotoxic T-cell immunity, and is characterized by infiltrates of oligoclonal T-cells in the CNS. Antibodies recognizing *cell-surface antigens* appear to directly cause paraneoplastic syndrome, maybe by disrupting normal synaptic transmission. Paraneoplastic syndromes may involve the peripheral or CNS, resulting in symptoms ranging from sensory neuropathies to profound and diverse neuropsychiatric disturbances, sometimes preceding the cancer diagnosis, including dysfunction in consciousness, cognition, behaviour, mood, and perception. *Limbic encephalitis*, one of the most common manifestations of paraneoplastic disorders, is characterized by rapid onset of neuropsychiatric symptoms that often culminate in severe neurological deterioration[60]. Other paraneoplastic neuropsychiatric syndromes include *epilepsia partialis continua* and *frontal disequilibrium.*

Metals Poisoning

Several *metals* have toxic actions on CNS, which can be expressed either as developmental effects or neurodegenerative diseases in old age. *Lead* exposure results in a shortened attention span and anti-social behaviour. *Mercury* has effects on cognition at low doses, while prenatal exposure at higher levels can disrupt brain development. Elevated *aluminium* levels in blood, usually resulting from kidney dialysis at home, result in dementia[61].

Neurological Disorder

Many neurologic conditions are associated with psychiatric manifestations, due to direct destroying action of expanding masses, vascular or immune-mediated damage and brain injury, or indirectly to intracranial hypertension, according to Monro-Kellie rule, finally secondarily to therapeutic efforts.

Head Trauma

Head injury represents the most common trauma typology in the ED. Acutely, *hypoxia* and *hypotension* due to airway/breath and circulation failure, according to ABCDE algorithm, may contribute to cerebral distress, which reveals oneself with amnesia, headache, sleepiness and coma[62]. *Intracranial hypertension* development causes vomiting, midriasis or anisocoria and movements deficit: the patient often seems restless and unable to understand what it happens. A CT scan is recommended in order to depict an *intracranial lesion*, chiefly epidural and subdural haematoma, contusions and intracranial haemorrhage. If the patient still remains conscious the cerebral lesion can develop in the following hours and reveals as a rapid cognitive decay and behavioural disorders. *Cerebral contusions* develop up to 30% of severe brain injuries, and can turn in intracranial haematomas, generally localized in frontal or temporal lobes. Tourette's syndrome, Huntington's disease, obsessive-compulsive disorder, attention-deficit/hyperactivity disorder, mood disorders and schizophrenia may result from any disturbances that have a direct or indirect impact on the integrity or functioning of the main frontal-subcortical circuits[63]. *Diffuse cerebral lesions,* ranging from the *mild brain concussions* to *severe hypoxic-ischemic forms*, generally show normal CT scan, while *diffuse axonal injury* can be detectable on CT scan as many dot-like haemorrhages. During rehabilitation after *traumatic brain injuries* may develop psychiatric disturbances, which can include alterations in behaviour and personality, sleep and emotional regulation, other than major depression, generalized anxiety disorder and post-traumatic stress disorder. Non-organic factors, including pre-morbid personality traits and post-injury psychological reactions to disability and trauma, are implicated in the generation and maintenance of post-traumatic brain injury psychiatric disorders, while there are insufficient evidence to conclude what role the neuropathological consequences play in their development[64].

Brain Neoplasia

Cognitive dysfunction and psychiatric disorders, due to the mass effect in particular sites (i.e.

frontal or temporal lobe) and/or the adverse effects of radiotherapy and chemotherapy, constitute a significant problem among *brain tumor* patients. Currently, it is considered the most frequent complication among long-term survivors[65].

Cerebral Vascular Accidents

Anxiety often accompanies a *TIA* and may be the major symptom of presentation in ED. Aphasia, unilateral neglect, anosognosia (deficit disorders), delirium and mood disorders (productive disorders), are the most frequent disorders checked during first examination of *stroke* in ED. Anxiety and depression are associated with left-hemispheric strokes. The left-side neglect and anosognosia are the most widespread neuropsychiatric symtoms after the right cerebral hemisphere lesion, and anxiety alone is commonly associated. Delirium ranges from 24 to 48% in acute stroke, and it is more frequent in haemorrhagic then ischemic form. Depression is a frequent post stroke consequence, especially if frontal lobe is involved, peaking three to six months after stroke[66]. Post-stroke mania should be considered in any old manic patient, overall showing concomitant neurological focal deficits. A systematic study of mania in acute stroke with subsequent follow-up and data from diffusion MR or perfusion CT is recommended[67].

Brain Inflammatory Diseases

Recent identification of syndromes encompassing psychiatric symptoms, seizures and movement disorders has led to effective treatments for several previously obscure conditions now known to be *immune-mediated encephalopathies,* predominantly associated with *cell surface antibodies*[47]. Main psychiatric manifestations in *limbic encephalitis* are irritability, depression, hallucinations, and personality disturbances, with neurocognitive changes in the form of short-term memory loss, sleep disorders, and seizures. Brain MR imaging usually demonstrates medial temporal lobe hyper-intensity, and CSF analysis reveals a mild lymphocytosis. Delayed recognition of autoimmune limbic encephalitis can result in long-term neuro-psychiatric consequences[68]. A potentially lethal, but treatment responsive *encephalitis* that associates with *NMDAr* was first described in 2007 in young women with teratomas, then also reported in men and children and without any detectable neoplasia. The clinical picture is initially characterized by psychiatric symptoms, such as consciousness impairment, hallucinations, and paranoid behaviour. The diagnosis is based on the clinical picture and supported by EEG, MR imaging and CSF analysis[69].

Brain Infectious Diseases

Brain suffering in *meningitis* and *encephalitis*, mainly of viral or bacterial etiology, together with common irritative signs and various neurological deficits, involves consciousness alterations (from sleepiness to coma) and psychiatric symptoms simulating anxiety (restlessness), mood disorders or true psychosis (delirium). Recent surveys have assessed a remarkable increase in the prevalence of infectious *syphilis*. If left untreated, 30% of patients may develop tertiary syphilis, with a variety of behavioural symptoms, agitation, mania, depression, manifest psychosis and frontal lobe dementia. Serum and CSF findings can reveal the presence of *Treponema pallidum* infection[70].

Brain Degenerative Diseases

Anxiety symptoms, depression and changes in personality are common in *Alzheimer's disease* or other forms of *dementia,* and sometimes precede the other early clinical manifestations, such as cognitive impairment and mood changes[71]. It is currently diagnosed by traditional or more recently developed criteria. Neuroimaging provides information about the topography and severity of vascular lesions in *vascular dementia*, revealing diffuse cerebral small-vessel disease, with extensive leukoencephalopathy or lacunae (basal ganglia or frontal white matter), single strategically located infarcts, or multiple infarcts in large-vessel territories[72]. *Reversible dementia* is a rare condition secondary to other cerebral or systemic diseases, and accounts for approximately 1.5% of all dementias[73]. Psychiatric manifestations are an integral part of *Huntington's disease*, including *specific* symptoms, such as the executive dysfunction syndrome, and *not-specific* symptoms, such as delirium. Anxiety and major depression have been reported as the most common prodromal symptom[74]. Although motor impairment constitutes the main finding of *Parkinson's disease,* sensorial, neurovegetative, cognitive and psychiatric symptoms may be more disabling than neurological symptoms. Depression, hallucinations and psychosis are more frequent hallmarks, especially in a more advanced stage[75]. Anxiety disorders are reported in 37% of patients with *multiple sclerosis*, but depression is the most frequently related disor-

der. In many cases multiple sclerosis is wrongly diagnosed as pure psychiatric disorder[76]. Also *Wilson's disease* may reveal itself as a neuropsychiatric disease in 40-50% of cases, including isolated behavioural problems, a schizophrenic syndrome, or a manic-depressive syndrome. Kayser-Fleischer's ring is almost constant among patients with neuropsychiatric features. MR imaging can show abnormal signals of the grey cores[77].

Toxic Encephalopathy

Common environmental neurotoxins, such as organic *industrial toxins* and *pesticides* (organophosphates and other compounds), other than select heavy metals, can cause encephalopathy, displaying behavioural and psychotic manifestations and cognitive impairment, variously associated to other organic symptoms. The importance of taking a good history and performing a comprehensive examination is emphasized. Neuroimaging and neurophysiologic testing play ancillary roles, while confirmatory laboratory tests are available only for some toxins[78].

Epilepsy

The relationship between *epilepsy* and psychiatric disorders, as well as their reciprocal influence, has been confirmed in several studies. Mood disorders are the most frequent conditions associated with epilepsy, followed by anxiety, attention-deficit, psychotic and personality disorders. Patients with *focal epilepsy*, and mainly those arising from temporal and frontal lobe, have a greater incidence of anxiety (panic attacks), depression, or psychosis[79]. *No-seizure epilepsy,* or *epilepsia partialis continua,* is a prolonged alteration of mental faculties for underlying epileptic cerebral activity showed on EEG, in absence of seizure. Clinical presentation may vary from a mild confusional state to simple sensitive symptoms (visual or auditive hallucinations) or complex (déjà vu), to behavioural disorders with panic or anger attacks, maniac-depressive episodes till quite psychotic pictures. It may have vascular, immune-mediated, neoplastic, metabolic or toxic causes, or constitutes a manifestation of Creutzfeldt-Jakob syndrome[80].

Hydrocephalus

Post-traumatic or idiopathic *adult chronic hydrocephalus* (so-called "*normal-pressure" hydrocephalus*) constitutes a neurosurgical cause of reversible dementia, easily revealed by brain CT scan[73]. Clinical picture is characterized by classic Adams triad: gait impairment, dementia and urinary incontinence. Hence, it can present with anxiety, paranoia, violent behaviour and psychosis, that may hinder its diagnosis[81]. The Othello syndrome, an obsessive love and delusional belief in the fidelity of a romantic partner, is also reported associated to adult chronic hydrocephalus[82].

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