Netherlands
The Journal of Medicine

REVIEW

The evaluation of spells

I.N. van Loon[1*], J. Lamberts[1], G.D. Valk[2], A.F. Muller[1]

[1]Department of Internal Medicine, Diakonessenhuis, Utrecht, the Netherlands, [2]Department of Internal Medicine, University Medical Centre Utrecht, Utrecht, the Netherlands, *corresponding author: tel.: +31 (0)88- 25 05 901, e-mail: i.n.vanloon@gmail.com

ABSTRACT

The differential diagnosis of spells is broad and includes both innocent and life-threatening conditions with a considerable overlap in clinical presentation. Extensive diagnostic testing is often performed, without reaching a final diagnosis, or resulting in false-positives. A thorough medical history, including family history and medication, and physical examination are required to obtain clues about the cause of a spell. An overview of spells with their stereotypic phenotype in general internal medicine practice is presented in this article. Besides, a diagnostic approach is proposed for the clinical evaluation of spells.

KEYWORDS

Spell, flushing, pheochromocytoma, gastroenteropancreatic neuroendocrine tumours, mastocytosis

Table 1. *Differential diagnosis of episodic symptoms*

Endocrine	**Pharmacological**
Pheochromocytoma	Abrupt withdrawal of adrenergic inhibitor
Thyreotoxicosis	MAO inhibitor in combination with specific food
Hypogonadism (menopause)	Sympathicomimetic
Medullary thyroid carcinoma	Hallucinating drugs (cocaine, LSD)
Pancreatic islet cell tumours (e.g. insulinoma, VIPoma)	Chlorpropamide-alcohol flush
Gastroenteropancreatic neuroendocrine tumours (carcinoid syndrome)	Vancomycin
Hypoglycaemia	Calcium antagonist
Cardiovascular	**Neurological**
Labile hypertension	Autonomic neuropathy
Pulmonary oedema	Migraine
Syncope	Epilepsy
Orthostatic hypotension	
Paroxysmal arrhythmias	**Other**
Angina pectoris	Mastocytosis
Renovascular disease	Recurrent idiopathic anaphylaxis
Psychiatric	
Panic disorder (hyperventilation syndrome)	
Conversion disorder	

INTRODUCTION

A spell is best defined as 'a sudden onset of a symptom or symptoms that are recurrent, self-limited, and stereotypic in nature'.[1] The differential diagnosis of spells is challenging and includes both innocent and life-threatening conditions with a considerable overlap in clinical presentation (*table 1*). This typically results in extensive diagnostic testing without reaching a final diagnosis, or in false-positives. In general, but especially in conditions with a differential diagnosis as extended as spells, testing for a particular disease should only be performed if the pre-test probability is high.

In this article we aim to provide a rational approach to the analysis of spells and spell-like symptoms for the general internist. First, we carried out a systematic literature search on the *systematic* evaluation of spells in general, thereby excluding manuscripts focusing on a specific disorder. Then, we described key components of history and physical examination that are necessary to make a differential diagnosis short list. A description of frequently encountered and commonly sought causes of spells is given. Finally, a proposed work-up for different types of spells is presented.

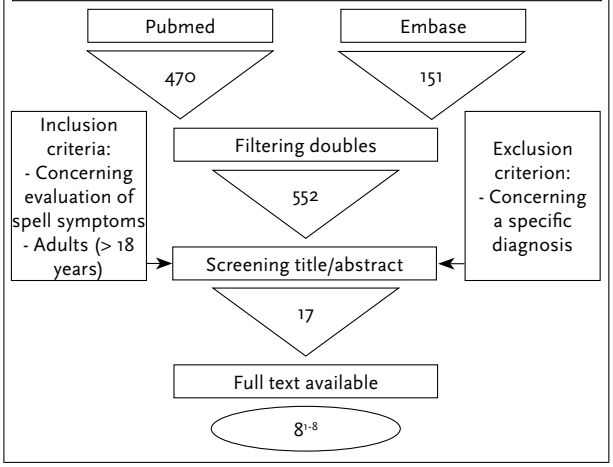
SEARCH STRATEGY

We searched PubMed and Embase databases for publications on the *systematic* evaluation of spells in general (i.e. manuscripts focusing on specific diseases were excluded in this stage) using synonyms for "spell" as shown in the syntaxes (*figure 1*). Since the terms "attack" and "attacks" resulted in many articles concerning neurological or cardiovascular disorders, but not in publications concerning spells in general, we decided to exclude these.

Figure 1. *Search strategy*

Pubmed: (Spell[title/abstract] OR spells[title/abstract] OR flush[title/abstract] OR flushing[title/abstract] OR flushing[MeSH] OR flushes[title/abstract] OR paroxysm[title/abstract] OR paroxysms[title/abstract])AND differential diagnosis[MeSH]

Embase: (Spell:ab,ti OR spells:ab,ti OR flush:ab,ti OR flushing:ab,ti OR flushes:ab,ti OR paroxysm:ab,ti OR paroxysms:ab,ti)AND 'differential diagnosis':ab,ti



When searching PubMed, we used Medical Subject Headings (MeSH terms) for differential diagnosis and flushing to broaden our search. Articles were considered relevant if they described a clinical syndrome fulfilling the criteria of a spell and the study subjects were at least 19 years of age. The search resulted in 17 apparently relevant articles, of which eight were available in full text.[1-8] Two of the articles were obtained by contacting the authors.[2,4] Three publications extensively describe the clinical evaluation of flushing.[5,7,8] Four articles describe a clinical case of a patient presenting with spells and work out the differential diagnosis.[3,6-8] Young *et al.* in particular describe pheochromocytoma, carcinoid syndrome and mastocytosis.[1] None of the publications found focus on the approach to the wide spectrum of spells in general internal medicine, including both rare and frequently observed conditions.

MAKING A DIAGNOSIS

History

The value of a detailed description of the spell cannot be overemphasised. Frequently the patient is able to provide sufficient information but, if this is not the case, it is imperative to obtain a detailed account from those who witnessed the event.

Establish what the patient was doing prior to the event, e.g. activities and position (upright, lying or changing position). Physical or psychological stressors immediately prior to the spell suggest a vasovagal event. Unusual smells, visual disturbances or uncontrolled movements may represent seizure activity, often referred to as an aura. If an attack starts with palpitations or tachycardia this suggests a cardiac cause. Loss or transient alteration of consciousness points to insufficient blood flow to the brain (syncope) or altered brain activity (generalised seizures).

Key components of the spell itself are a description of the specific symptoms, sequence of occurrence, timing, frequency and duration. Besides all of the above, it is important to determine factors which provoke, exacerbate or relieve the attack, such as heat, medications or alcohol. If the attack is accompanied by flushing, one should determine whether it is a 'wet' or a 'dry' flush. A 'wet' flush – e.g. the postmenopausal hot flash – is accompanied by sweating and is of a neurogenic nature (mediated by sympathetic cholinergic neurons that also stimulate sweat glands) whereas a 'dry' flush is the result of direct vasodilatation due to either endogenous (e.g. histamine, prostaglandin and polypeptides) or exogenous (e.g. nicotinic acid an amyl nitrite) substances and is not associated with perspiration.[1] Patients presenting with evident neurological spell-like symptoms are generally referred to the neurologist. It is important to realise that a number of internal diseases, such as porphyria and carcinoid syndrome, can also be accompanied by neurological or psychiatric symptoms. Hypoglycaemia may present with neurological symptoms due to neuroglycopenia. Loss of, or decreased consciousness, may be triggered by cerebrovascular diseases, hypoglycaemia or cardiac arrhythmias. A period of lethargy after the spell can indicate mastocytosis or epilepsy. Listing current medication including recent changes can give important clues pointing to a correct diagnosis, especially in the geriatric population with polypharmacy. Medication associated with flushing is shown in *table 2*.

Regarding family history special attention should be paid to sudden death, hormonal, neurological, psychiatric and sleep disorders.

Physical examination

A key element of the physical examination of a patient presenting with episodic symptoms is the measurement of blood pressure and pulse rate, preferably during the attack. Attention should be paid to the presence of orthostasis, tachycardia and/or an irregular heartbeat. The classical presentation of a pheochromocytoma is intermittent hypertension, but orthostatic hypotension may also occur.[9,10] Orthostatic hypotension may cause episodic dizziness. The thyroid is examined for goitre or palpable nodules. Cardiac murmurs and pulmonary wheezing may be an indication of carcinoid syndrome, which is associated with pulmonary valve stenosis and tricuspid regurgitation,

Table 2. *Medical history and findings*

Spell history
Description of specific symptoms
Sequence of occurrence, timing, frequency, duration of symptoms
Wet flush, dry flush or episodic pallor
Hypertension over time
Lethargy after the spell
Provoking, exacerbating or relieving factors
Cardiac complaints: chest pain, fatigue, dyspnoea, dizziness
Neurological complaints: weakness, sensory loss, altered states of consciousness
Medication
Family history and social history
Physical examination
Blood pressure
Pulse rate and rhythm
Determine orthostatic hypotension
Thyroid goitre or nodules
Cardiac examination: murmurs, deviated ictus cordis
Abdominal examination: Hepatosplenomegaly, abdominal murmur
Skin: urticaria pigmentosa, body hair distribution
Genitalia: testis atrophy

caused by endocardial fibrosis.[11] A deviated ictus cordis, sign of ventricular hypertrophy, can be found in patients with carcinoid syndrome or pheochromocytoma. Examination of the abdomen may reveal hepatomegaly or splenomegaly. The first can be found in metastatic disease (i.e. neuroendocrine tumour), or cardiac failure, whereas isolated splenomegaly may be caused by mastocytosis.[12] An abdominal murmur can indicate pheochromocytoma. The skin is inspected for urticaria pigmentosa (reddish-brown maculae or papules in mastocytosis), and hair pattern, which may differ in hypogonadism. In males suspected of hypogonadism the testis should be examined for testis atrophy.

Mental status can also give important clues. With syncopal events patients quickly regain consciousness whereas post-spell confusion is more typical of a seizure.

DIFFERENTIAL DIAGNOSIS

After taking the history and performing a physical examination, the key elements of which are listed in *table 3,* a differential diagnosis must be made in order to provide guidance in the ordering and interpretation of diagnostic tests. However, given the diversity of diseases and the overlap in clinical presentation we – and others[1] – recommend the following initial laboratory investigations: complete blood count with differential, serum electrolytes, glucose, creatinine, calcium, phosphorus, liver function tests, thyroid-stimulating hormone, luteinising hormone, follicle-stimulating hormone, testosterone or oestradiol, and urine analysis. Further testing should be directed by the differential diagnosis.

Table 3. *Medication associated with flushing (Izikson et al.)*[2]

All vasodilators: nitroglycerin and nitric oxide releasers: e.g. sildenafil	Cholinergic drugs	Vancomycin
All calcium channel blockers	Bromocriptine	Rifampicin
Calcitonin	Chemotherapeutics: cyclosporine, doxorubicin, cisplatin, interferon alfa-2	Contrast media
Beta-blockers	Anti-androgens: flutamide, cyproterone	Combination anaesthesia of isoflurane and fentanyl
Angiotensin-converting enzyme inhibitors	Anti-oestrogens: tamoxifen	Morphine and other opiates
Catecholamines	Prostaglandins	Antiemetics: e.g. metoclopramide
NSAIDs	Caffeine withdrawal	In combination with alcohol: disulfiram, metronidazole, ketoconazole, cephalosporins, anti-malarials
Triamcinolone	Alcohol withdrawal	
Methylprednisolone	Nicotine	

Episodic flushing and palpitations often characterise or accompany an attack. We have therefore designed two decision trees, which can guide in the diagnosis of these symptoms (*figures 2* and *3*). Carcinoid syndrome flushing can last from seconds to hours, usually located in the

Figure 2. *Decision tree for palpitations*

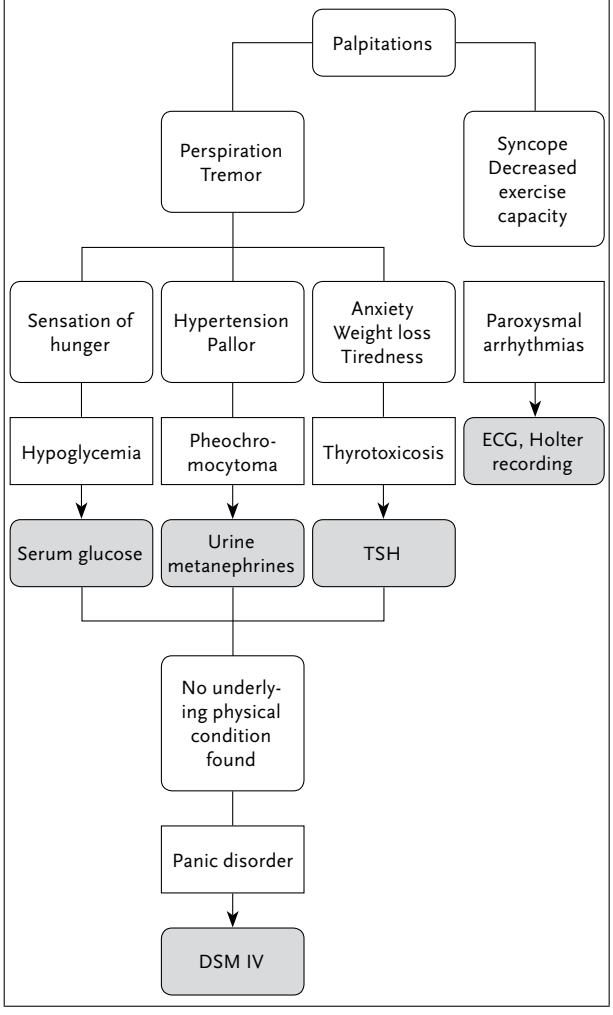
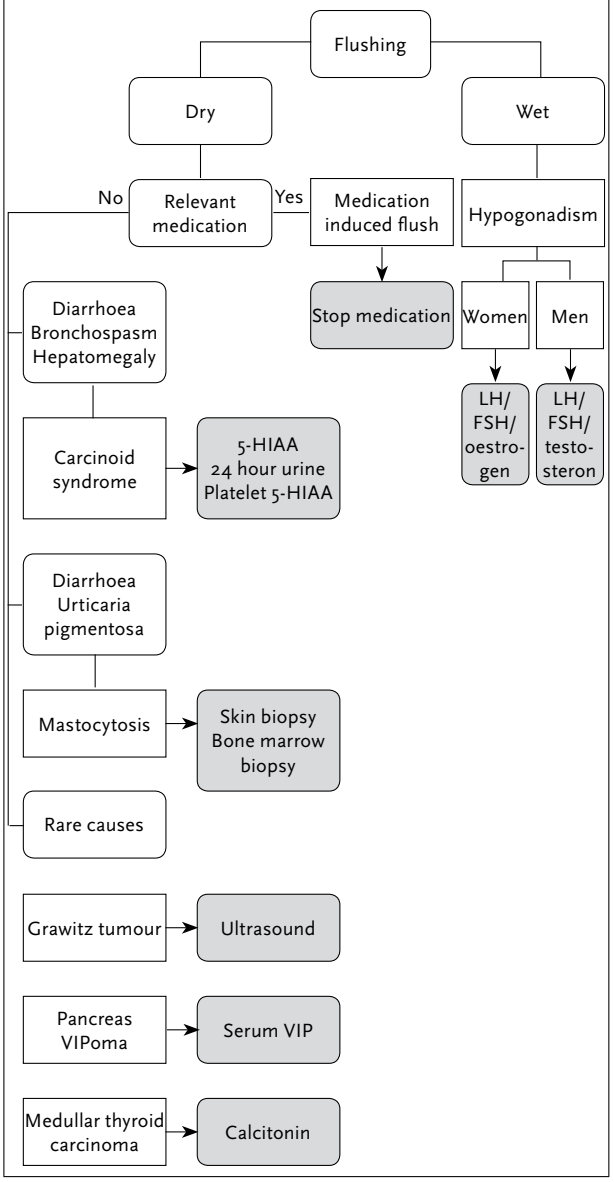


Figure 3. *Decision tree for flushing*



upper half of the body, pink-red to vermilion or dusky blue and may be spontaneous, induced by eating, alcohol, movement or necrosis of tumour deposits.[13] In case of mastocytosis, attacks usually last 15 to 30 minutes with flushing and facial warmth and associated with palpitation, light-headedness and even syncope.

SPECIFIC DISORDERS

In this section we provide some basic information regarding some of the frequently described causes of spells. *Table 4* summarises classical spell phenotypes of these causes. The spell-like symptoms they comprise are listed in *table 5*. Additional diagnostic testing is shown in *table 6*.

Table 4. *Classical spell phenotypes*

Disease	Classic features
Pheochromocytoma	Triad: headaches, palpitations, sweating. Hypertension, pallor
Thyrotoxicosis	Fatigue, anxiety, sweating, palpitations
Mastocytosis	Urticaria pigmentosa, dry flushing, diarrhoea, abdominal pain
Carcinoid syndrome/ GEP-NET	Dry flushing, diarrhoea, bronchospasm, enlarged liver
Hypogonadism	Hot/wet flushes, sweating
Hypoglycaemia	Hunger, tremor, weight gain, symptoms disappear after a meal
Porphyria	Colicky abdominal pain, neurological symptoms
Panic attack	Psychological component, palpitations, chest pain, shortness of breath
Paroxysmal arrhythmias	Palpitations

Hypogonadism – 'Hot flashes'

Hot flashes are a sensation of heat associated with vasodilation and a drop in body temperature. Frequently associated symptoms are: sweating, flushing, palpitations, anxiety, irritability and panic.[14] It is the most common symptom of premenopausal and postmenopausal women.[14] Men on androgen deprivation therapy also have this symptom.[14] In the differential diagnosis of hypogonadism, a distinction is made between primary (ovarian/testicular) and secondary (pituitary/hypothalamic) lack of sex hormones. The pathophysiology of hot flashes is largely unknown.[14] The heat sensation lasts for four minutes on average with a wide variation from seconds to as long as ten minutes.[14] The frequency of such hot flash varies, from several times a day to several times a week.[14] It is important to note that a postmenopausal woman with this typical pattern of complaints is virtually always suffering from climacteric hypogonadism and the diagnosis is a clinical one based on menstrual history and age.[15]

Panic disorder

Panic disorder is a treatable psychiatric disorder which is quite common, with a prevalence of 4 to 7%.[16] Panic disorder is characterised by recurring severe panic attacks and may include ongoing worry about the implications or concern about having other attacks.[16] There are various symptoms: palpitations, chest pain, sweating, shortness of breath, feelings of suffocation and dizziness may occur. In addition, patients experience a fear of dying or doing something uncontrollable during an attack. The criteria of panic disorder according to the Diagnostic and statistical manual of mental disorders (DSM-IV-R) are listed in *table 7*.[17]

After appropriate testing to rule out medical conditions psychiatric referral is in order, especially since 90% of patients with panic disorder will have at least one other psychiatric diagnosis during their lifetime.[16]

Table 5. Occurrence of episodic symptoms

	Pheochromocytoma	Thyrotoxicosis	Mastocytosis	Carcinoid syndrome	Hypogonadism	Hypoglycaemia	Porphyria	Paroxysmal arrhythmias	Panic attack
Weight loss	+/-	+	-	-	-	-	-	-	-
Tachycardia	+/-	+	-	-	-	+	+/-	+	+
Palpitations	++	++	-	-	+	++	+/-	++	++
Tremor	+	+	-	-	-	++	+/-	-	+
Perspiration	++	+	-	-	++	+	+/-	-	+
Flushing	-	-	++	++	++	-	-	-	-
Hypertension	++	+/-	-	-	-	-	+/-	+	-
Abdominal pain	-	+/-	++	++	-	-	++	-	+
Diarrhoea	-	+/-	++	++	--	--	-	--	+/-

-- = never; - = seldom; +/- = sometimes; + = often; ++ = classical symptom.

Table 6. *Additional testing*

Disease	Additional diagnostics
Pheochromocytoma	Plasma free metanephrines or urine fractionated metanephrines
Thyrotoxicosis	TSH, free T4
Mastocytosis	Main criterion: mast cell aggregates of > 15 in bone marrow. Additional criteria: - atypical mast cell morphology - abnormal immunophenotype (CD2,CD25,CD35) - serum tryptase - codon 816 mutation of c-kit cells in affected tissue. For diagnosis: main criterion with an additional criterion, or three additional criteria. Alternative: - urine histamine - skin biopsy: urticaria pigmentosa
GEP-NET/ Carcinoid syndrome	- HIAA in 24-hour urine Platelet 5-HIAA
Hypogonadism	LH, FSH Male: testosterone Women: oestrogen
Hypoglycaemia	Fasting glucose Glucose, insulin, C-peptide, proinsulin, beta-hydroxybutyrate and circulating oral hypoglycaemic agents
Porphyria	Porphobilinogen in 24-hour urine
Panic attack	None
Paroxysmal arrhythmias	ECG, Holter recording

Table 7. *Criteria for diagnosis of panic disorder*[17]

Recurrent unexpected panic attack, defined as a discrete period of intense fear or discomfort in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes:
Palpitations, pounding heart
Sweating
Trembling or shaking
Shortness of breath or choking
Feeling of choking
Chest pain or discomfort
Nausea or abdominal distress
Feeling dizzy, light-headed, or faint
Derealisation or depersonalisation
Fear of losing control or going crazy
Fear of dying
Chills or hot flushes
Paresthesias

At least one of the attacks followed by one month (or more) of one (or more) of the following:
Persistent concern about having additional attacks
Worry about the implications of the attack or its consequences
A clinically significant change in behaviour related to the attacks

Panic attacks not due to the direct physiological effects of an illicit substance (or a prescribed medication) or a general medical condition (e.g., hyperthyroidism)

Panic attacks not better accounted for by another mental disorder, such as social phobia (on exposure to a feared social situation), a specific phobia (during exposure to a specific situation that prompts a phobic response), post-traumatic stress disorder (in response to stimuli associated with a severe stressor), or separation anxiety disorder (in response to being away from home or from a close relative)

Diagnostic and Statistical Manual of Mental Disorders, 4th edition

Systemic mastocytosis

Mastocytosis is characterised by an abnormal increase in the number of tissue mast cells.[12] Mast-cell disease is most commonly seen in the skin, but the skeleton, bone marrow, gastrointestinal tract, and central nervous system may also be involved.[12] In up to 20% of cases syncope and flushing, caused by degranulation of mast cells, is a prominent symptom.[18] A typical attack usually lasts 15 to 30 minutes, and can be accompanied by flushing, dyspepsia, diarrhoea, abdominal pain, musculoskeletal pain, hypotension and syncope.[1] Precipitating factors are: heat, exertion, emotion, sexual arousal and medications such as aspirin and

opioids. An attack can be followed by a period of lethargy. In 90% of patients the skin is involved, manifested by pruritus, urticaria pigmentosa (a red brown macular rash with a wheal and flare reaction) and dermatographism.[18] Therefore, the finding of urticaria pigmentosa in a patient evaluated for unexplained flushing points to a diagnosis of mastocytosis.[4]

Diagnosis is established by demonstration of mast cell proliferation in involved tissues. Biopsy of an urticaria pigmentosa lesion is the least invasive way to obtain histology.[19] Otherwise a bone marrow biopsy with immunohistochemical staining against mast cell markers (CD117 and tryptase) is indicated as this test is positive in about 90% of cases. An alternative approach is to search for elevated levels of biochemical markers of mast cell activation such as serum tryptase or urine histamine and its metabolites.[20,21]

Pheochromocytoma

Pheochromocytoma is a catecholamine-producing tumour arising from the chromaffin cells of the adrenal medulla, or sympathetic ganglia (paraganglioma).[9] Hypertension is not always present but can be paroxysmal and some patients present with hypotension and orthostatic hypotension.[9,22] Symptoms include a traditional triad of headaches, palpitations and sweating with a specificity of 90% when present together.[9,22] A typical pheochromocytoma spell usually lasts 10 to 60 minutes with a wide frequency of occurrence from daily to several times per year.[1] Pallor is more common than flushing with a reported frequency of 40 to 45%; flushing occurs in 10 to 20% of cases only and is due to primary epinephrine and dopamine secretion or a cosecreted peptide such as vasoactive intestinal polypeptide.[1,9] Other signs and symptoms may include nausea, weight loss, tiredness, anxiety or panic, papilla oedema with loss of vision, weight loss, hyperglycaemia, polyuria, polydipsia, increased haematocrit, and cardiomyopathy.[1,9]

Hereditary pheochromocytomas occur in paraganglioma syndromes, multiple endocrine neoplasia type 2, Von Hippel-Lindau syndrome, neurofibromatosis type 1 and paraganglioma syndromes. Frequently, however, pheochromocytoma is not the first manifestation and often other typical symptoms are present.[9]

Diagnosis depends on biochemical evidence of catecholamine overproduction of the tumour and is best based on plasma-free metanephrines or metanephrines and normetanephrines in 24-hour urine specimens.[23,24] The sensitivity of plasma-free metanephrines for the detection of a pheochromocytoma is 99% with a specificity of 89%.[9,23] If determination of plasma metanephrines is unavailable, then the second best diagnostic test is urinary fractionated metanephrines (normetanephrine and metanephrine separately) with a sensitivity and specificity of 97% and 69% respectively.[12,16] However, mildly elevated catecholamines and/or metanephrines may be aspecific and this further aggravates the diagnostic challenge.[25]

Gastroenteropancreatic neuroendocrine tumours

Gastroenteropancreatic neuroendocrine tumours (GEP-NET) are solid tumours arising from the diffuse endocrine system. They originate from enterochromaffin or the closely related enterochromaffin-like cells, present in most organs but primarily in the submucosa of the gut (67%, where they are most common in small intestine (25%), appendix (12%), and rectum (14%)[26]) and the respiratory system.[27] The incidence is estimated at 1 to 2 per 100,000, but is probably higher, since many GEP-NET are indolent, and may secrete hormonal peptides, without the characteristics of a clinical syndrome (nonfunctioning neuroendocrine tumours). This was confirmed by a recent study which showed a substantial discrepancy in numbers of diagnosed GEP-NET between a clinical and a pathological setting.[28]

Neuroendocrine tumours can produce various signalling proteins, of which serotonin (i.e. 5-hydroxytryptamine) is the most prominent. Other substances that may be released include histamine, dopamine, substance P, neurotensin, prostaglandins and kallikrein. Carcinoid syndrome occurs when liver or lung metastases have formed and metabolism of these neurosecretory substances is impaired, thereby causing significant release into the systemic circulation. This includes both episodic symptoms and those signs and symptoms due to structural changes induced by these substances.[13] The medullary thyroid carcinoma and pancreatic VIPoma may present with flushing due to secretion of calcitonin and vasoactive intestinal peptide respectively. Both diseases are also associated with chronic diarrhoea, although VIPoma in particular causes massive diarrhoea. Flushing mainly occurs in medullary thyroid carcinoma when metastases have developed.

Presentation varies with the embryological origin of the tumour, but carcinoid syndrome is mainly associated with neuroendocrine tumours of the stomach and ileum. Typical symptoms are attacks of flushing, diarrhoea and wheezing.[13] A 'carcinoid spell' can be provoked by exercise, or ingestion of blue cheese, chocolate (both containing tyramine) and alcohol. The flush may last from seconds up to hours and is associated with a mild burning sensation, predominantly affecting the upper body half with colour changes from blush pink to blue.[13] As the disease progresses, the flushing periods may become longer and more diffuse and cyanotic. In severe cases tachycardia, hypotension and angio-oedema may be present.[13] Carcinoid heart disease is characterised by pathognomonic plaque-like deposits of fibrous tissue. These deposits occur most commonly on the endocardium

of valvular cusps and leaflets, the cardiac chambers, and occasionally on the intima of the pulmonary arteries or aorta.[11] The right side of the heart is most often affected.[29,30]

The 5-hydroxyindoleacetic acid (5-HIAA) urinary level in a 24-hour sample is most commonly used in the endocrine workup of neuroendocrine tumours.[31,32] However, inference with drugs and food products is common.[31,32] Platelet serotonin is a more discriminating marker for the diagnosis of neuroendocrine tumours, especially in foregut tumours, where urine serotonin may have a poor sensitivity.[33,34]

Thyrotoxicosis

Thyrotoxicosis is a condition showing an excess of circulating thyroid hormone, which activates the adrenergic system.[35] The incidence is 0.5%, with Graves' disease and toxic nodular goitre comprising the majority of new cases.[35-37] Patients may suffer from palpitations, tremor, heat sensitivity, irregular menses in women, anxiety or nervousness.[35,36] In addition, more non-specific symptoms such as fatigue and weight loss may be seen.[35,36] Episodic symptoms can be caused by cardiac arrhythmias which, when present, require thyroid function testing especially in the elderly.[38] Due to the high prevalence of thyrotoxicosis, it may be difficult to establish if symptoms are fully explained by the thyrotoxicosis. In this respect subclinical thyrotoxicosis is only very rarely the cause of significant symptoms.

Hypoglycaemia

Hypoglycaemia raises adrenergic activity, resulting in classical symptoms such as sweating, anxiety, tremor, palpitations, tachycardia, hunger and nausea. If left untreated, neuroglycopenia occurs, resulting in dizziness, headache, visual disturbances, confusion, and ultimately coma and even death.[39,40] Blood glucose lowering drugs and alcohol are the most common causes of hypoglycaemia.[39,41] In critically ill patients, sepsis, renal, hepatic and adrenal failure should be investigated as causes of hypoglycaemia.[39] In patients with a history of gastric bypass surgery, hypoglycaemia resulting from nesidioblastosis is recognised.[42,43] Thus, unexplained spells post-bariatric surgery should raise suspicion of hypoglycaemia. Another less frequent cause of hypoglycaemia is insulinoma. This rare condition should be suspected in patients in which the Whipple's triad is positive (i.e. symptoms of hypoglycaemia, severe hypoglycaemia documented during the attack, relief from the attack by administering glucose.[39,42] Finally, one should always bear in mind that hypoglycaemia can be factitious or even felonious.[39,41]

With regards to diagnosis, it is essential to document hypoglycaemia before pursuing a differential diagnosis of hypoglycaemia. In a patient suspected of insulinoma, a supervised fast should be carried out, with measurement of glucose, insulin, C-peptide, proinsulin, beta-hydroxybutyrate and circulating oral hypoglycaemic agents. When symptoms of hypoglycaemia occur, this should then be corrected with 1.0 mg of glucagon iv with subsequent measurement of glucose. The response will most likely establish diagnosis.[39,40] In an asymptomatic patient in whom fasting hypoglycaemia is suspected a prolonged (72-hour) supervised fast is indicated. When the history is suggestive of postprandial hypoglycaemia an appropriate meal should be served to the patient;[39] for an interpretation of the test result, see *table 3* from Cryer et al.[39]

Porphyria

Porphyria includes several hereditary disorders with a defect in the haeme biosynthetic pathway, with accumulation of porphyrin precursors as a result.[44] One of these conditions is acute intermittent porphyria, classically presenting with colicky abdominal pain and a range of neurological symptoms. Fever, tachycardia, sweating, tremor and hypertension may also be present.[44] In addition, psychiatric symptoms may occur.[45] The urine turns red due to excretion of the precursors of haeme synthesis.[44] A spell can be triggered by various stressors, including alcohol, infections, menstruation, and various medications.[44] Diagnosis is established by demonstrating a markedly increased urinary porphobilinogen in a urine specimen.[44]

Paroxysmal arrhythmias

An underlying cardiac arrhythmia is the most common cause of palpitations. The severity of the clinical symptoms depends on the remaining cardiac output. Decrease in cardiac function can lead to clinical symptoms such as breathlessness, chest pain and syncope. Paroxysmal arrhythmias may also occur in other conditions such as thyrotoxicosis, pheochromocytoma, hypoglycaemia and panic attacks. The mutual underlying pathophysiological mechanism is increased activity of the adrenergic system. Syncope is usually benign but can be the only warning symptom before an episode causing sudden death.[46] If a syncopal event is suspected, an electrocardiogram is indicated[47] and will lead to a diagnosis in 2 to 11% of cases.[47,48] Other causes of transient loss of consciousness are epilepsy, psychogenic disorders and several rare miscellaneous disorders.[49]

DISCUSSION

Some common conditions presenting with episodic symptoms will rarely cause diagnostic problems. Hot flushes in combination with age and menstrual pattern in

women, or in combination with prescribed anti-androgen therapy in men, will usually be readily explained by hypogonadism. In daily practice, most episodes of hypoglycaemia occur in patients known to have diabetes mellitus. If the patient is not known to have diabetes a full work-up is clearly indicated. Tachycardia and palpitations are most common in paroxysmal cardiac arrhythmias or panic disorders. However, in any patient presenting with these complaints, the exclusion of hyperthyroidism as an underlying cause with a single determination of the TSH level is appropriate.

In the category of patients with a more complex spell phenotype resembling pheochromocytoma, carcinoid syndrome or mastocytosis, diagnosis is far more difficult. Hopefully, the tables and figures we present in this overview will provide some guidance.

CONCLUSION

Patients who present with a spell represent a diagnostic challenge. History and physical examination are essential in obtaining clues about the cause of the spell. Hereafter the use of other diagnostic tests should be guided by the differential diagnosis.

REFERENCES

1. Young WF Jr, Maddox DE. Spells: in search of a cause. Mayo Clin Proc. 1995;70:757-65.
2. Izikson L, English JC, Zirwas MJ. The flushing patient: differential diagnosis, workup, and treatment. J Am Acad Dermatol. 2006;55:193-208.
3. Khoo TK, Service FJ. 47-Year-old woman with spells of slurred speech, blurred vision, and loss of consciousness. Mayo Clin Proc. 2006; 81:1495-8.
4. Metcalfe DD. Differential diagnosis of the patient with unexplained flushing/anaphylaxis. Allergy Asthma Proc. 2000;21:21-4.
5. Mohyi D, Tabassi K, Simon J. Differential diagnosis of hot flashes. Maturitas. 1997;27:203-14.
6. Scully RE. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 7-1992. A 57-year-old man with a 20-year history of episodic headache, Flushing, hypotension, and occasional syncope. N Engl J Med. 1992;326:472-81.
7. Stehouwer CD, Gans RO. [Clinical thinking and decision-making in practice. A patient with episodes of flushing]. Ned Tijdschr Geneeskd. 1999;143:792-6.
8. Suchard JR. Recurrent near-syncope with flushing. Acad Emerg Med. 1997;4:718-24.
9. Lenders JW, Eisenhofer G, Mannelli M, Pacak K. Phaeochromocytoma. Lancet. 2005;366:665-75.
10. Samuels MA, Pomerantz BJ, Sadow PM. Case records of the Massachusetts General Hospital. Case 14-2010. A 54-year-old woman with dizziness and falls. N Engl J Med. 362:1815-23.
11. Pandya UH, Pellikka PA, Enriquez-Sarano M, Edwards WD, Schaff HV, Connolly HM. Metastatic carcinoid tumor to the heart: echocardiographic-pathologic study of 11 patients. J Am Coll Cardiol. 2002;40:1328-32.
12. Golkar L, Bernhard JD. Mastocytosis. Lancet. 1997; 349:1379-85.
13. Hodgson HJF. Carcinoid tumours and the carcinoid syndrome. In: Wass JAH, Shapiro MD, editors. Oxford textbook of endocrinology and diabetes. Oxford: Oxford University Press, 2002.
14. Stearns V, Ullmer L, Lopez JF, Smith Y, Isaacs C, Hayes D. Hot flushes. Lancet. 2002; 360:1851-61.
15. Bastian LA, Smith CM, Nanda K. Is this woman perimenopausal? JAMA 2003;289:895-902.
16. Katon WJ. Clinical practice. Panic disorder. N Engl J Med. 2006;354:2360-7.
17. Diagnostic and statistical manual of mental disorders. 4th ed rev.: DSM-IV-R ed. Washington, DC: American Psychiatric Association, 2000.
18. Shome GP, Nangia R, Baldwin JL. Flushing and syncopal episode in a 47-year-old female. Ann Allergy Asthma Immunol. 2001;86:161-5.
19. Topar G, Staudacher C, Geisen F, et al. Urticaria pigmentosa: a clinical, hematopathologic, and serologic study of 30 adults. Am J Clin Pathol. 1998;109:279-85.
20. Granerus G, Olafsson JH, Roupe G. Studies on histamine metabolism in mastocytosis. J Invest Dermatol. 1983;80:410-6.
21. Schwartz LB, Metcalfe DD, Miller JS, Earl H, Sullivan T. Tryptase levels as an indicator of mast-cell activation in systemic anaphylaxis and mastocytosis. N Engl J Med. 1987;316:1622-6.
22. Plouin PF, Degoulet P, Tugaye A, Ducrocq MB, Menard J. [Screening for phaeochromocytoma : in which hypertensive patients? A semiological study of 2585 patients, including 11 with phaeochromocytoma (author's transl)]. Nouv Presse Med. 1981;10:869-72.
23. Lenders JW, Pacak K, Walther MM, et al. Biochemical diagnosis of pheochromocytoma: which test is best? JAMA. 2002; 287:1427-34.
24. Pacak K, Linehan WM, Eisenhofer G, Walther MM, Goldstein DS. Recent advances in genetics, diagnosis, localization, and treatment of pheochromocytoma. Ann Intern Med. 2001;134:315-29.
25. Bisschop PH, Corssmit EP, Baas SJ, et al. Evaluation of Endocrine Tests. C: glucagon and clonidine test in phaeochromocytoma. Neth J Med. 2009;67:91-5.
26. Modlin IM, Kidd M, Latich I, Zikusoka MN, Shapiro MD. Current status of gastrointestinal carcinoids. Gastroenterology. 2005;128:1717-51.
27. Lechago J. Gastrointestinal neuroendocrine cell proliferations. Hum Pathol. 1994;25:1114-22.
28. Kuiper P, Verspaget HW, Overbeek LI, Biemond I, Lamers CB. An overview of the current diagnosis and recent developments in neuroendocrine tumours of the gastroenteropancreatic tract: the diagnostic approach. Neth J Med. 2011; 69:14-20.
29. Lundin L, Norheim I, Landelius J, Oberg K, Theodorsson-Norheim E. Carcinoid heart disease: relationship of circulating vasoactive substances to ultrasound-detectable cardiac abnormalities. Circulation. 1988; 77:264-9.
30. Pellikka PA, Tajik AJ, Khandheria BK, et al. Carcinoid heart disease. Clinical and echocardiographic spectrum in 74 patients. Circulation. 1993; 87:1188-96.
31. Feldman JM. Urinary serotonin in the diagnosis of carcinoid tumors. Clin Chem. 1986; 32:840-4.
32. Sjoblom SM. Clinical presentation and prognosis of gastrointestinal carcinoid tumours. Scand J Gastroenterol 1988; 23:779-87.
33. Onaitis MW, Kirshbom PM, Hayward TZ, et al. Gastrointestinal carcinoids: characterization by site of origin and hormone production. Ann Surg. 2000;232:549-56.
34. Meijer WG, Kema IP, Volmer M, Willemse PH, de Vries EG. Discriminating Capacity of Indole Markers in the Diagnosis of Carcinoid Tumors. Clin Chem. 2000; 46:1588-96.
35. Cooper DS. Hyperthyroidism. Lancet. 2003;362:459-68.
36. Brent GA. Clinical practice. Graves' disease. N Engl J Med. 2008;358:2594-605.

37. Muller AF, Berghout A, Wiersinga WM, Kooy A, Smits JW, Hermus AR. Thyroid function disorders--Guidelines of the Netherlands Association of Internal Medicine. Neth J Med. 2008;66:134-42.

38. Boelaert K, Torlinska B, Holder RL, Franklyn JA. Older subjects with hyperthyroidism present with a paucity of symptoms and signs: a large cross-sectional study. J Clin Endocrinol Metab. 95:2715-26.

39. Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2009; 94:709-28.

40. Service FJ. Hypoglycemic disorders. N Engl J Med. 1995; 332:1144-52.

41. Marks V, Teale JD. Hypoglycemia: factitious and felonious. Endocrinol Metab Clin North Am. 1999;28:579-601.

42. Service GJ, Thompson GB, Service FJ, Andrews JC, Collazo-Clavell ML, Lloyd RV. Hyperinsulinemic hypoglycemia with nesidioblastosis after gastric-bypass surgery. N Engl J Med. 2005;353:249-54.

43. Bernard B, Kline GA, Service FJ. Hypoglycaemia following upper gastrointestinal surgery: case report and review of the literature. BMC Gastroenterol. 2010; 10:77.

44. Anderson KE, Bloomer JR, Bonkovsky HL, et al. Recommendations for the diagnosis and treatment of the acute porphyrias. Ann Intern Med. 2005;142:439-50.

45. Auchincloss S, Pridmore S. Vomiting, burns, and irrational behaviour. Lancet. 2001;358:1870.

46. Grubb BP. Clinical practice. Neurocardiogenic syncope. N Engl J Med. 2005;352:1004-10.

47. Preblick-Salib C, Jagoda A. Spells. Differential diagnosis and management strategies. Emerg Med Clin North Am. 1997;15:637-48.

48. Day SC, Cook EF, Funkenstein H, Goldman L. Evaluation and outcome of emergency room patients with transient loss of consciousness. Am J Med. 1982;73:15-23.

49. Moya A, Sutton R, Ammirati F, et al. Guidelines for the diagnosis and management of syncope (version 2009): the Task Force for the Diagnosis and Management of Syncope of the European Society of Cardiology (ESC). Eur Heart J. 2009; 30:2631-71.