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Cleveland Clinic Center for Continuing Education

Flushing

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Definition

Flushing describes episodic attacks of redness of the skin together with a sensation of warmth or burning of the face, neck and, less frequently, the upper trunk and abdomen. It is the transient nature of the attacks that distinguishes flushing from the persistent erythema of photosensitivity or acute contact reactions. Repeated flushing over a prolonged period can lead to telangiectasia and occasionally to classic rosacea of the face.[1]

Flushing can be an exaggeration of a physiologic process or a manifestation of a serious condition that needs to be identified and treated. A biochemical workup of every case of flushing is neither practical nor cost-effective; in this chapter, we present guidelines that will help determine when a workup is warranted.

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Prevalence

The prevalence of flushing has not been determined.

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Pathophysiology

Redness of the skin may be caused by an increased amount of saturated hemoglobin, an increase in the diameter or actual number of skin capillaries, or a combination of these factors.[2] Flushing is caused by increased blood flow through the skin, causing warmth and, because of engorgement of the subpapillary venous plexus, redness. The vasodilation of flushing may be caused by a direct action of a circulatory vasodilator substance—for example, histamine—or it may be caused by changes in the neurologic control of the cutaneous vasculature in the affected areas. In the face, neck, and upper trunk, where flushing is most frequent, the neurologic control of vascular tone is predominantly exerted by autonomic vasodilator nerve fibers. These fibers are found in somatic nerves supplying the affected skin, including the trigeminal nerve. Because autonomic nerve fibers also supply eccrine sweat glands, neurally activated flushing is frequently associated with sweating (wet flushing) as opposed to flushing caused by circulating vasodilator mediators, which frequently does not involve sweating (dry flushing). The presence or absence of sweating has therefore been proposed as a clinical guide to the mechanisms of flushing, although in practice this is not always reliable. Examples of wet flushing are physiologic flushing and menopausal flushing. An example of dry flushing is niacin-provoked flushing.[1]

The diameter of the blood vessels of the cheeks is wider than elsewhere, the vessels are nearer to the surface, and there is less tissue thickness obscuring them. This may explain why flushing occurs in that limited distribution.[3] Polycythemia produces the characteristic ruddy complexion, but it may also cause a peculiar coloration termed *erythremia*, which is a combination of redness and cyanosis. The tongue, lips, nose, earlobes, conjunctivae, and fingertips especially demonstrate this coloration. Erythremia results when there is a combination of increased amounts of saturated and desaturated hemoglobin.

In some carcinoid tumors, fibrosis of the right side of the heart may lead to a combination of stenosis and regurgitation at the tricuspid valve, as well as pulmonary stenosis. If cyanosis occurs, the combination of flushing and cyanosis may produce the reddish cyanotic erythremia.[2]

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Flushing Syndromes

Physiologic Flushing

Embarrassment or anger may cause flushing in some individuals in whom the threshold for this response may be low or the reaction itself unusually intense; this is also known as blushing.[1,2] Explanation and reassurance are usually sufficient. If necessary, propranolol or nadolol may be used to alleviate the symptom.[1]

Heat causes flushing in many patients, and overheating can lower the threshold to flushing from other causes, such as menopause.[3] Overheating, such as after exercise or sauna, can cause physiologic flushing because of the effect of the rise in blood temperature on the thermoregulatory center in the anterior hypothalamus. A similar mechanism is responsible for facial flushing caused by hot drinks, which produce a rise in temperature of blood in the oral cavity, in turn leading to an increase in temperature of blood perfusing the hypothalamus. The temperature of hot coffee, rather than its caffeine, causes flushing.

A useful maneuver for patients faced with a brief thermal exposure is to suck on ice chips carried in an insulated cup. This attenuates flushing for the first 20 to 30 minutes.[3]

Menopausal Flushing

About 80% of postmenopausal women experience flushing associated with sweating. A similar syndrome may also occur in men with prostate cancer receiving treatment with gonadotropin-releasing hormone analogues, such as buserelin. About 65% of postmenopausal women have hot flushes for 1 to 5 years, 26% for 6 to 10 years, and 10% for more than 11 years. There is considerable variation in the frequency, intensity, and duration of hot flushes within and among individuals.

A typical hot flush begins with a sensation of warmth in the head and face, followed by facial flushing that may radiate down the neck and to other parts of the body; it is associated with an increase in temperature and pulse rate and followed by a decline in temperature and profuse perspiration over the area of flush distribution. Visible changes occur in about 50% of women. Each hot flush lasts for 1 to 5 minutes.

The primary role of estrogen deficiency has been questioned and a deficit of thermoregulation has been proposed. Rapid estrogen withdrawal rather than a low estrogen level by itself is likely to induce hot flushes.[4] Synchronous with the onset of each hot flush is the release of a pulse of luteinizing hormone; this does not seem to be responsible for the hot flush, because flushing can occur after hypophysectomy. The anterior hypothalamus has estrogen and progesterone receptors, and both hormones can be used effectively to treat hot flushes through binding with their respective hypothalamic receptors. Neurotransmitters that may be involved in the pathogenesis of hot flushes include norepinephrine and other noradrenergic substances. The central noradrenergic system in the hypothalamus triggers the hot flushes via α_2-adrenergic receptors on the noradrenergic neurons. Thus, clonidine, an α_2-adrenergic agonist, effectively alleviates hot flushes through reduction of noradrenergic release.[4]

Pharmacologic menopause with flushing can be induced by various drugs 4-hydroxyandrostenedione, danazol, tamoxifen, clomiphene citrate, and leuprolide. Certain characteristics suggest the diagnosis of climacteric flushing, such as drenching perspiration, a prodromal sensation of overheating before the onset of flushing and

sweating, and waking episodes at night, with the typical symptoms. Alcohol can enhance a menopausal flush.[5] Veralipride, an antidopaminergic drug, can cause reductions in the frequency and intensity of menopausal flushing in premenopausal women pretreated with goserelin (a gonadotropin-releasing hormone agonist) for endometriosis.[6]

Flushing Caused by Drugs

Other medications that can cause flushing are corticotropin- releasing hormone, doxorubicin, and niacin (Box 1). Flushing is a side effect of sildenafil citrate in 12% of patients.[7] Systemic administration of morphine can cause flushing of the face, neck, and upper shoulders, which is believed to be histamine-mediated.[5] Patients can develop facial flushing, generalized erythema, or both after epidural or intra-articular administration of glucocorticoids. The exact pathophysiology is unclear but could be related to distention of the joint capsule.[8]

Box 1 Flushing Caused By Drugs

All vasodilators (e.g., nitroglycerin, prostaglandins)

All calcium channel blockers

Nicotinic acid (not nicotinamide)

Morphine and other opiates

Amyl nitrite and butyl nitrite

Cholinergic drugs (e.g., metrifonate, anthelmintic drug)

Bromocriptine used in Parkinson's disease

Thyrotropin-releasing hormone (TRH)

Tamoxifen

Cyproterone acetate

Oral triamcinolone

Cyclosporine

Rifampin

Sildenafil citrate

Adapted from Cutaneous manifestations of disorders of the cardiovascular and pulmonary systems. In Freedberg IM, Eisen AZ, Wolff K, et al (eds): Fitzpatrick's Dermatology in General Medicine, 5th ed, vol 2. New York, McGraw-Hill, 1999, pp 1935-1945.

Flushing Associated with Alcohol Intake

Asians with certain genotypes show extensive flushing in response to low doses of alcohol. They have been found to have higher plasma levels of acetaldehyde. This abnormality is probably related to a deficiency of an isoenzyme of liver aldehyde dehydrogenase. This population can be detected by using an ethanol patch test, which produces localized erythema. A special type of alcohol flush is also associated with chlorpropamide, the oral antihyperglycemic agent. Even small amounts of alcohol provoke intense flushing within a few minutes of ingestion. This flushing is not associated with sweating but, in some cases, tachycardia, tachypnea, and hypotension may be seen. The flush is mediated by elevated acetaldehyde plasma levels and possibly by the

release of prostaglandins. Alcohol ingestion can also trigger flushing in those with carcinoid tumors, mastocytosis, medullary thyroid carcinoma, and certain lymphoid tumors.

Trichloroethylene, a chemical that has been abandoned in recent years because of its carcinogenic potential, can cause flushing. When inhaled following ingestion of alcoholic beverages, a striking cutaneous reaction results, consisting in the sudden appearance of erythema of the face, neck, and shoulders, a reaction that has been termed *degreaser's flush*. Nausea and vomiting can also occur.[5]

Flushing Associated with Food

Eating spicy or sour foods can cause facial flushing. This gustatory flushing is caused by a neural reflex involving autonomic neurons carried by the branches of the trigeminal nerve. The flushing may be unilateral.

The flushing of monosodium glutamate (MSG) is controversial. Oral challenge with MSG has failed to provoke flushing in volunteers with a history of MSG flushing. Patients should be encouraged to look beyond MSG at other dietary agents, such as red pepper, other spices, nitrites and sulfites (additives in many foods), thermally hot foods and beverages, and alcohol.[5] Scombroid fish poisoning (tuna and mackerel) is caused by the ingestion of fish that was left in a warm temperature for hours. In addition to flushing, patients with scombroid fish poisoning experience sweating, vomiting, and diarrhea. These symptoms are caused by intoxication with histamine, which is believed to be generated by histidine decarboxylation by bacteria in spoiled fish.

Carcinoid Syndrome

Carcinoid syndrome describes the manifestations of carcinoid tumors-flushing, bronchoconstriction, gastrointestinal hypermotility, and cardiac disease. Carcinoid tumors are neuroendocrine tumors derived from a primitive stem cell that may differentiate into any of various adult endocrine-secreting cells, producing peptides, hormones, and neurotransmitters. The annual incidence is 1.5 per 100,000 population.[9] The average age of patients is 50 years, and there is no gender predominance.[10]

Carcinoid syndrome occurs in about 10% of patients with these tumors.[10] In 75% of patients, episodes of severe flushing are precipitated by exercise, alcohol, stress, and certain foods (e.g., spices, chocolate, cheese, avocados, plums, walnuts,[1] red sausage, red wine). With time, the flushing may appear without provocation.[9] The character of the flush differs, depending on the site of origin of the tumor (Figs. 1 and 2). Tumors of the foregut (stomach, lung, pancreas) are associated with a bright red geographic flush of a more sustained duration, as well as lacrimation, wheezing, sweating, and a sensation of burning. In ileal tumors, the flush is patchier and more violaceous, intermingled with areas of pallor, and does not last as long. Flushing of either type may be associated with facial edema, which may persist and lead to telangiectasia and even facial rosacea. With extensive disease, pellagra-like skin lesions can also be seen; these result from excessive uptake of tryptophan by the carcinoid tumor, leaving little for the daily niacin requirement. These lesions include hyperkeratosis, xerosis, scaling of the legs, forearms, and trunk, angular cheilitis, and glossitis (Fig. 3). Seventy percent of patients also have watery diarrhea, and 35% develop right-sided endocardial fibrosis, leading to congestive heart failure. Diarrhea and other gastrointestinal manifestations may precede or coexist with the flushing.[5]

Ninety-five percent of all carcinoids are found in the appendix, rectum, or small intestine.[9] The remainder arise outside of the intestinal tract (e.g., in the ovary or testis). In general, the larger the primary tumor, the greater the likelihood of metastasis, which provides prognostic implications.[9] Carcinoids of the appendix and rectum rarely manifest with the carcinoid syndrome. Forty percent to 50% of patients with carcinoids of the small intestine or proximal colon have manifestations of the carcinoid syndrome.[10] Tumors that secrete their hormonal product into the portal venous system do not cause flushing, because the released amines are inactivated by the liver. In contrast, liver metastases may escape hepatic inactivation and deliver their product directly into the systemic circulation, hence causing flushing.[9] Pulmonary or ovarian carcinoids release pharmacologic products directly

into the venous circulation, bypassing the portal system, and can therefore cause symptoms without metastasizing to the liver.[1,10]

Pathophysiology

The flushing seen with foregut carcinoids is caused by the release of histamine. Flushing seen with ileal carcinoids cannot be explained solely by the production of serotonin.[1] Serotonin may or may not be released into the circulation during flushing, and IV infusion of serotonin does not cause flushing. Foregut carcinoids do not generally secrete serotonin but, instead, its precursor, 5-hydroxytryptamine. Screening should therefore seek this product if the other metabolites are not elevated.[9] Other mediators that have been proposed include prostaglandins and tachykinins. Tachykinins are believed to be mediators of the flushing in tumors of the midgut. They exert vasodilation and contraction of various types of smooth muscle. These peptides include substance P, substance K, and neuropeptide K. Urine excretion of histamine is usually increased in patients who have gastric carcinoids (Table 1).[9]

Table 1 Classification of Carcinoid Tumors According to Site of Primary Tumor

Site	Biochemistry	Clinical Picture
Foregut bronchi, stomach, first part duodenum	5-Hydroxytryptophan, adrenocorticotropin, growth hormone, gastrin, growth hormone releasing hormone	Protracted, purplish or violaceous flush, manifestation of other ectopic hormone secretion
Midgut second part of duodenum, jejunum, ileum, ascending colon	Serotonin, kinins, neuropeptides, prostaglandins	Pink-red flush
Hindgut transverse, descending colon and rectum	None	Only local symptoms

Adapted from Vinik AI: Neuroendocrine tumors of carcinoid variety. In DeGroot LJ (ed): Endocrinology, 3rd ed, vol 3. Philadelphia, WB Saunders, 1995, pp 2803-2812.

Diagnosis

Clinical diagnosis is not difficult in patients with flushing episodes associated with systemic symptoms (e.g., diarrhea, wheezing, weight loss) and hepatomegaly. It is more difficult in patients who have occasional flushing and no associated symptoms.[1] Only when there is reasonable clinical suspicion should biochemical testing be done, and localization studies must be reserved for those cases proven biochemically.[10] When in doubt, a carcinoid flush can be provoked by alcohol ingestion (4 mL of 45% ethanol) or the infusion of 6 µg noradrenaline, an effect that can be blocked by phentolamine (5-15 mg IV). Calcium gluconate, 10 to 15 mg/kg, administered IV over 4 hours, may produce a flush mimicking a spontaneous attack.[5] Epinephrine reverses flushing in patients with mastocytosis but provokes flushing in patients with the carcinoid syndrome. The procedure should only be performed in a controlled environment. A 1-µg/mL solution of epinephrine in normal saline is administered by an IV bolus, beginning with an initial dose of 0.05 µg. The dose is doubled at intervals of 10 minutes until flushing appears or until a maximum of 6.4 µg is given. When flushing occurs, it usually begins within 60 seconds after epinephrine administration and dissipates after 3 or 4 minutes.[10]

The diagnosis should be confirmed by determining urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of serotonin, which is normally 2 to 10 mg (10-50 µmol)/24 hours.[5] A value of more than 150 µmol/24 hours (30 mg/24 hours) usually confirms the diagnosis, and in carcinoid syndrome it is often above

40 mg/day.[5] This test has a sensitivity of 75% and a specificity of up to 100%. The degree of elevation of 5-HIAA does not always correlate with the severity of flushing.[9] Excretion fluctuates, so that repeat measurements may be necessary. Some patients with carcinoid may lack the metabolic machinery to convert serotonin to 5-HIAA, so they have high blood levels of serotonin but normal urinary 5-HIAA levels.[5] Dietary factors may cause confusion; the patient should therefore receive a diet free of the culprit items (Box 2) for 3 days before the urine collection is made. Although the levels of serotonin in patients with tumors usually far exceed those found after food ingestion, this precaution helps exclude carcinoid in individuals with borderline high 5-HIAA levels.[9] Measuring the blood serotonin level is helpful when the urinary 5-HIAA level is equivocal. Patients with carcinoid syndrome have very high blood levels of serotonin. Measurement of serotonin and its metabolites permits the detection of 84% of neuroendocrine tumors. Even carcinoids that predominantly secrete 5-hydroxytryptophan are associated with increased urinary excretion of 5-HIAA because the released 5-hydroxytryptophan is converted to serotonin in other tissues and is subsequently metabolized to 5-HIAA.[9] Chromogranin A, a peptide cosecreted with serotonin, is elevated in most patients with carcinoid tumors. In the evaluation of flushing with an equivocal 24-hour urinary 5-HIAA level, a normal plasma chromogranin A value suggests nonendocrine causes. This test is sensitive but not specific, and its predictive value in carcinoid is still uncertain.[10] Flushing was associated with a rise in circulating substance P in 80% of patients with gastric carcinoid. Neurokinin A levels are elevated in certain patients (Box 2 and Box 3).[9]

Box 2 Factors that Can Precipitate Flushing in the Carcinoid Syndrome

Foods and Beverages

Hot foods or beverages

Spicy foods

Chocolate

Cheeses

Tomatoes

Avocados

Red plums

Walnuts

Eggplant

Alcohol

Other Causes

Emotional stress

Valsalva maneuver

Straining

Vigorous coughing

Sudden direct pressure on a large carcinoid tumor

Adapted from Cutaneous manifestations of disorders of the cardiovascular and pulmonary systems. In Freedberg IM, Eisen AZ, Wolff K, et al (eds): Fitzpatrick's Dermatology in General Medicine, 5th ed, vol 2. New York, McGraw-Hill, 1999, pp 1935-1945.

Box 3 Factors that Interfere with Determination of Urinary 5-HIAA

Factors that Produce False-Positive Results

Foods

Avocados

Bananas

Eggplants

Pineapples

Plums

Walnuts

Drugs

Acetaminophen

Acetanilid

Caffeine

Fluorouracil

Guaifenesin

Lugol's (iodine) solution

Melphalan

Mephenesin

Methamphetamine

Methocarbamol

Methysergide maleate

Phenacetin

Phenmetrazine

Reserpine

Factors that Produce False-Negative Results

Drugs

Corticotropin

p-Chlorophenylalanine

Chlorpromazine

Heparin

Imipramine

Isoniazid

Methenamine mandelate

Methyldopa
Monoamine oxidase inhibitors
Phenothiazine
Promethazine
Methenamine mandelate

5-HIAA, 5-hydroxyindoleacetic acid.

Adapted from O'Toole D, Ducreux M, Bommelaer G, et al: Treatment of carcinoid syndrome: A prospective crossover evaluation of lanreotide versus octreotide in terms of efficacy, patient acceptability, and tolerance. Cancer 2000;88:770-776.

Treatment

Corticosteroids, phenothiazines, and bromocriptine have been effective in the treatment of patients with bronchial carcinoid tumors. The mechanism of action of these agents is unknown. Cyproheptadine, a serotonin antagonist, may control the flushing. Methysergide can control the diarrhea but has no effect on flushing. Combined administration of histamine types 1 and 2 (H_1 and H_2) receptor antagonists may prevent attacks of flushing in patients with foregut carcinoid tumors that produce histamine.[10] Alpha-interferons may control symptoms of carcinoid syndrome and produce objective biochemical responses (>50% suppression of 5-HIAA) with a median duration of approximately 4 weeks.10 Because catecholamines are known to precipitate attacks, a trial of clonidine is worthwhile. Somatostatin is a potent antagonist of the flushing reaction associated with both gastric and ileal carcinoid tumors but has a short half-life. The somatostatin analogue octreotide has a much longer half-life, making subcutaneous therapy possible. It must be given by subcutaneous injection one to three times/day and should be titrated in increments of 50 µg every 8 hours.[10] Octreotide lowers plasma levels of serotonin and tachykinins and relieves flushing and diarrhea. Amelioration of these manifestations is accompanied by a marked reduction in the urinary excretion of 5-HIAA.[10] Lanreotide, a long-acting analogue of somatostatin administered IM every 14 days, is effective at controlling the flushing of carcinoids.[11,12] A depot form of octreotide (Sandostatin LAR Depot) has been shown to control flushing at a dose of 20 mg IM every month.[13] Flushing may relapse with continued treatment.[9] The patient should receive an adequate niacin supplement (nicotinamide rather than nicotinic acid, because the latter causes flushing) and should avoid foods, agents, and activities that precipitate symptoms.[5]

In some patients, failure of medical treatment may necessitate carrying out hepatic artery embolization. This treatment is based on the dependence of metastatic malignant tissue but not healthy liver parenchyma on an intact hepatic arterial blood supply. Antitumor chemotherapy remains experimental. Alpha-interferon causes symptomatic relief accompanied by lowering of the urinary 5-HIAA level.

Prognosis

Approximately 20% of patients with the carcinoid syndrome undergo a protracted course. In the remainder, deterioration can be rapid. The mean survival is about 8 years, with some surviving up to 20 years. Mean survival is 36 months after the first flushing episode.[9]

Mastocytoses

Causative Factors

Mastocytoses are benign proliferative disorders of the reticuloendothelial system and familial cases have been reported. Mastocytoses are caused by a hyperplastic rather than neoplastic process. They are often self limited, especially in childhood (Box 4). Mast cells contain the enzyme histidine decarboxylase, which enables them to synthesize and store histamine. Other preformed mediators include tryptase, chymase, and carboxypeptidase. Serotonin has not been detected in human mast cells.[14]

Box 4 Classification of Mastocytoses

Benign

Cutaneous

Urticaria pigmentosa

Solitary mastocytoma

Diffuse and/or erythrodermic (systemic involvement common; can be fatal)

Telangiectasia macularis eruptiva perstans

Systemic

Myeloproliferative, myelodysplastic

Gastrointestinal

Skeletal

Malignant

Lymphadenopathic with eosinophilia

Mast cell leukemia

Histopathology

There are increased numbers of normal-looking mast cells in the dermis. These cells may be predominantly perivascular or may show a nodular distribution. The epidermis is normal, apart from increased melanization.[14]

Biochemical Markers

Symptoms of mastocytosis are mainly the result of release of products of mast cell activation. Plasma histamine levels are frequently increased in patients with systemic symptoms, and elevated urinary excretion of histamine and its metabolite methyl imidazole acetic acid (MIAA) can also be seen. Plasma tryptase levels can also be elevated. Prostaglandin D_2 (PGD_2) is another product of mast cell activation. Urinary excretion of this substance and its major metabolites can be elevated severalfold in patients with mastocytoses. Urine should be collected within a few hours of an attack.[14]

Clinical Presentation

Episodic bright red flushing occurs spontaneously or after rubbing the skin or exposure to alcohol or mast cell degranulating agents. Flushing attacks may be accompanied by headache, dyspnea and wheezing, palpitations, abdominal pain, diarrhea, and syncope and may closely resemble the flushing episodes of the carcinoid syndrome, especially the foregut variety, which are also mediated by histamine. Rosacea may develop rarely. PGD_2 might be associated with the symptoms of flushing and diarrhea.[14] The flushing of cutaneous

mastocytosis typically lasts more than 30 minutes, unlike the typical carcinoid flush, which lasts less than 10 minutes.[5] In urticaria pigmentosa, the diagnosis is established by demonstrating that gentle rubbing of the lesional skin causes local itching, redness, and whealing (Darier's sign). This reaction is caused by local histamine release. Darier's sign may also be demonstrated in skin without lesions. Confirmation of the diagnosis is obtained by skin biopsy. In patients with systemic symptoms, bone marrow biopsy and liver and spleen scans are usually performed. Bone scans should only be carried out in the presence of localized bone symptoms.[5,14]

Treatment

Treatment of nonlocalized forms of mastocytosis is mainly symptomatic. Patients should avoid known histamine-degranulating agents. Antihistamines remain the preferred treatment for most patients with uncomplicated urticaria pigmentosa. Human skin blood vessels possess H_1 and H_2 receptors, which are involved in both vasodilation and increased vascular permeability evoked by histamine. Thus, combination treatment with an H_1 antihistamine (hydroxyzine 10-20 mg) and H_2 antihistamine (cimetidine 200-500 mg) is logical and sometimes effective at controlling the flushing episodes. Oral administration of the mast cell stabilizing agent disodium cromoglycate has proved effective in some patients. The drug does not decrease urinary excretion of histamine and the histamine metabolite MIAA. Some experts have recommended using this agent only in patients with systemic mastocytosis who suffer from gastrointestinal symptoms. Photochemotherapy has been reported to cause symptomatic relief as well as objective reduction in the population of mast cells and the urinary excretion of MIAA.[14]

Medullary Thyroid Carcinoma

The range of substances secreted by medullary carcinoma of the thyroid is considerable, whether sporadic or familial. Flushing is the most common symptom after diarrhea. Occurring in one third of the patients with diarrhea, there is pronounced episodic flushing, which, as in the carcinoid syndrome, may be induced by alcohol ingestion. Calcitonin gene-related peptide, which is an extremely powerful peripheral vasodilator, is the most likely mediator that causes flushing.[5] The other possible explanation is that calcitonin stimulates prostaglandins, which in turn cause the symptoms.[12]

Harlequin Syndrome

This describes hemifacial flushing and sweating sometimes associated with warmth and anhidrosis of the contralateral arm and leg (Fig. 4). This may be induced by exercise. The suggested cause is a lesion involving preganglionic or postganglionic cervical sympathetic fibers and parasympathetic neurons of the ciliary ganglion.[15] Harlequin syndrome has been described in patients with a contralateral lung cancer invading the spine, Pancoast's syndrome, and Horner's syndrome.[5]

Auriculotemporal Nerve Syndrome (Frey's Syndrome)

This syndrome usually manifests as immediate unilateral or bilateral flushing, sweating in the distribution of the auriculotemporal nerve, or both in response to gustatory or tactile stimuli. In adults, this syndrome is a well-recognized sequela of parotid surgery, trauma, or infection. It occurs rarely in children, most often noted after the introduction of solid food. The flushing is often attributed erroneously to food allergy. It typically begins at 2 to 6 months of age when solid foods, mostly fruit, are introduced. Occurring within a few seconds of eating, it has a peculiar distribution in a triangular area that extends from the tragus of the ear to the midpoint of the cheek. It is not associated with sweating and persists for 20 to 60 minutes. The flushing continues to occur for up to 5 years. In adults, gustatory sweating is the predominant feature of auriculotemporal nerve syndrome; flushing happens less often. One half of pediatric patients with this symptom were delivered with forceps assistance, which possibly causes trauma to the nerve. The likely mechanism is misdirection of parasympathetic fibers along

sympathetic pathways during the nerve regeneration that follows trauma. This may account for erythema when eating. The emergence of symptoms several months after the proposed trauma (usually 3-6 months) is probably related to the time required for nerve regeneration, and it is possible that vigorous chewing causes intense stimulation of the parotid gland. Auriculotemporal nerve syndrome is benign in infants and does not tend to worsen. Furthermore, the severity of the flushing tends to diminish with age in most patients. The physician can reassure parents and avoid unnecessary testing and maneuvers (Fig. 5).[16] A similar syndrome can develop after facial herpes zoster.[17]

Flushing with Pseudocarcinoid Syndrome in Secondary Male Hypogonadism

A series of three male patients with secondary hypogonadism has been described, in whom flushing was associated with elevated 24-hour urine 5-HIAA levels. Flushing disappeared, and 5-HIAA levels normalized after starting testosterone enanthate treatment. Male patients with flushing and increased urinary 5-HIAA levels should undergo assessment for hypogonadism after screening for carcinoid tumor.[18]

Treatments that lower the serum testosterone level, such as orchiectomy or luteinizing hormone-releasing hormone analogues, cause hot flushes in more than 50% of men. Lack of regulatory feedback in the hypothalamus from circulating serum testosterone is the presumed mechanism. Most often, hot flushes are only mildly bothersome and can be tolerated without the need for treatment. However, if flushes are particularly annoying or problematic, treatment should be offered. Small doses of diethylstilbestrol are effective in relieving hot flushes but cause gynecomastia. Megestrol acetate, 20 mg twice daily, completely eliminates hot flushes in most men, and the dose can be progressively lowered in some.[19]

Other Diseases Causing Episodic Flushing

Cheung and colleagues[20] have described a family with monoamine oxidase deficiency causing episodes of flushing affecting the face and chest precipitated by emotion or certain foods, followed by diarrhea, headaches, and sometimes palpitations. Blood serotonin levels in this family were elevated secondary to decreased activity of monoamine oxidase. Sertraline hydrochloride controlled the symptoms by depleting platelet serotonin.

Flushing is rare in patients with pheochromocytoma. If flushing occurs at all, it is seen after a paroxysm of hypertension, tachycardia, palpitations, chest pain, severe throbbing headaches, and excessive perspiration. Pallor is typically present during the attack, and mild flushing may occur after the attack as a rebound vasodilation of the facial cutaneous blood vessels.[5] Facial flushing and headache can happen along with sweating of the face, neck, and upper trunk in patients with spinal cord lesions above T6. This may occur as an exaggerated response to bowel or bladder distention.[1] Other causes are certain pancreatic tumors, insulinoma, and POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal proteinemia, and skin changes). Transient flushing of the face, chest, or arms has been noted after neurologic deterioration secondary to a rapid increase in intracranial pressure.[21]

Rosacea

Persistent flushing from any cause may eventually lead to rosacea. The lesions of rosacea that initially occur in the central convex areas of the face consist of papules and pustules against a background of erythema, telangiectasia, edema, and eventual permanent induration or thickening of affected skin.[2] Patients with severe flushing caused by mastocytosis can develop rosacea in less than 1 year after the onset of flushing episodes.[5]

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Evaluation Of The Patient With A Flushing Disorder

It is important to consider the clinical characteristics of the flushing before embarking on expensive laboratory evaluation.[5] The physician should consider four clinical characteristics in the initial evaluation of a patient with flushing: provocative and palliative factors, morphology, associated features, and temporal characteristics.[2]

Provocative or Palliative Factors. Certain agents that trigger the flush suggest an underlying systemic disease as the cause for the flushing, such as mastocytosis and carcinoid syndrome.

Morphology

- Is there a basic feature that comes and goes?
- Is the redness patchy or confluent?
- What is the color of the flush?
- Is there cyanosis?
- Is the flushing preceded or followed by pallor?[2]

The morphology of the flushing may suggest not only the cause of the flushing but also, in the case of carcinoids, the anatomic origin of the disorder.[5]

Associated Features. Associated features may include respiratory symptoms, gastrointestinal symptoms, headache, urticaria, facial edema, hypertension, hypotension, palpitations, or sweating.

Temporal Characteristics. Temporal characteristics are the frequency of the flushing and the timing of the specific features during each flushing reaction. Important information can be obtained from a 2-week diary in which the patient records qualitative and quantitative aspects of the flushing event and lists exposure to all exogenous agents.[2] When the diagnosis remains obscure after evaluation of the 2-week diary, the patient is given an exclusion diet listing foods high in histamine, foods and drugs that affect urinary 5-HIAA tests, and foods and beverages that cause flushing. If the flushing reactions completely disappear, restoring the excluded items individually can identify the causative agent. If the flushing reactions continue unchanged, then further metabolic workup may be undertaken.[5]

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Summary

- It is important to differentiate physiologic flushing from flushing associated with more serious diseases.
- Distinguish wet flushing from dry flushing.
- Look for flush distribution, triggers, reproducibility, and associated symptoms.
- Do not forget to look for drugs that are known to cause flushing.
- Alcohol and certain foods can cause physiologic flushing but may also trigger flushing in carcinoid syndrome.
- The character of the flushing in carcinoid syndrome depends on the location of the tumor.

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Suggested Readings

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