Flushing in relation to a possible rise in intracranial pressure: documentation of an unusual clinical sign

Report of five cases

GREGORY W. HORNSG, M.D.

Department of Neurosurgery, Children’s Mercy Hospital, University of Missouri, Kansas City, Missouri

This report documents clinical features in five children who developed transient reddening of the skin (epidermal flushing) in association with acute elevations in intracranial pressure (ICP). Four boys and one girl (ages 9–15 years) deteriorated acutely secondary to intracranial hypertension ranging from 30 to 80 mm Hg in the four documented cases. Two patients suffered from ventriculoperitoneal shunt malfunctions, one had diffuse cerebral edema secondary to traumatic brain injury, one was found to have pneumococcal meningitis and hydrocephalus, and one suffered an intraventricular hemorrhage and hydrocephalus intraoperatively. All patients were noted to have developed epidermal flushing involving either the upper chest, face, or arms during their period of neurological deterioration. The response was transient, typically lasting 5 to 15 minutes, and dissipated quickly. The flushing reaction is postulated to be a centrally mediated response to sudden elevations in ICP. Several potential mechanisms are discussed. Flushing has clinical importance because it may indicate significant elevations in ICP when it is associated with neurological deterioration. Because of its transient nature, the importance of epidermal flushing is often unrecognized; its presence confirms the need for urgent treatment.

Key Words • intracranial hypertension • pediatric neurosurgery • epidermal flushing • hydrocephalus • head injury

any clinical syndromes and physical signs have been described as relating to elevations in ICP with or without concomitant brain herniation. In the later stages of increased ICP, stupor and coma occur in association with cardiorespiratory changes, including elevation of BP, bradycardia, and irregularity of respiratory rhythm, resulting in the well-known Cushing reflex.5 The Cushing reflex is less frequently observed in children than in adults. The signs more typically seen with elevation of ICP in a pediatric population include neck rigidity, sunsetting or loss of upward gaze, scalp vein distention, tense anterior fontanelle, splayed cranial sutures, papilledema, acute strabismus, distended retinal veins, rapidly increasing head circumference, and pupillary changes, usually accompanied by changes in the level of consciousness. Typical symptoms include irritability, vomiting, drowsiness or lethargy, headache, and anorexia.

Other less common clinical signs indicate significant elevations in ICP. These include profuse sweating, acute pulmonary edema, pupillary dilation and ipsilateral hemiplegia (Charcot triad), visual obstructions, optic nerve atrophy, sixth, seventh, and 12th cranial nerve palsies, Cheyne–Stokes respirations, bilateral extensor plantar responses, decorticate or decerebrate posturing, Parinaud syndrome, neurogenic stridor, and pseudobulbar paresis.9

To our knowledge, only one published report briefly describes a macular rash on the extensor surfaces of the limbs of three children with progressive hydrocephalus whose rash occurred “at the same level of ICP on each occasion.”9 There were 107 cases reviewed in that report and epidermal flushing was distinctly unusual, occurring in fewer than 3% of children with acute elevations in ICP.

We present five pediatric patients who developed a transient cutaneous macular flush in association with acute elevation in ICP. Case 1 involves a child treated at another institution whose clinical course we were asked to review in the course of defending against litigation. A compelling history of transient epidermal flushing directly preceding herniation occurred in this case; this was the red flag that heightened our sensitivity to the association of elevated ICP and flushing in the four children treated subsequently by us.

Case Report

Case 1

This 14-year-old boy who had a history of hydrocephalus and a VP shunt in place presented with complaints of severe headache, nausea, vomiting, and intermittent somnolence. He had undergone two shunt revisions within 3
Flushing in relation to a rise in intracranial pressure

weeks. He was admitted for observation, and a shunt revision was planned. Prior to his operation, he could answer questions appropriately and was arousable, but remained uncomfortable because of his headache. He had a sweating episode and stated that he was cold. One hour later he was noted by his nurse to be “screaming that [his head] hurt so bad.” His BP was 200/100 mm Hg and his HR was 98 bpm. The nurse reported that he quickly became unresponsive and developed a bright red rash over his trunk. The episode was documented to last approximately 10 minutes, after which the rash dissipated, his BP fell to 140/80 mm Hg, his HR was 58 bpm, and he became more arousable. Less than 1 hour later he was again unresponsive and vomiting, and he was rushed to surgery, because he had become obtunded and had developed fulminating pulmonary edema. He underwent intubation and a shunt revision was performed. Postoperatively he exhibited symptoms consistent with central and transcaline herniation, with significant motor, visual, and cognitive deficits. Although no direct pressure measurements were reported, ICP elevations most likely occurred because of shunt malfunction.

Case 2

This 10-year-old boy who had a history of congenital hydrocephalus for which a VP shunt had been placed was found to be obtunded and was brought to the emergency department for evaluation of possible shunt malfunction. On arrival, he was awake and responsive to verbal commands. His CT scan showed moderate ventricular dilation that was less than that observed on a preshunt study obtained 10 years previously. Shortly after arrival in the emergency department he was noted to become increasingly unresponsive and he developed a macular erythematous rash that spread from his face to his chest and upper arms. This flushing-type response resolved with hyperventilation via bag and mask. His level of consciousness improved, but after a few minutes he again developed the flushing erythema. He developed a classic Cushing response with an HR in the 40s and BP of 150/102 mm Hg. His pupils were 5 mm and sluggishly reactive bilaterally. He underwent emergency intubation by the rapid sequence method, received hyperventilation, and was taken to the operating room for shunt revision. He was found to have a distal shunt obstruction. At the time of surgery his ventricular pressure was measured directly with a manometer and was in excess of 500 mm Hg ( > 37 mm Hg). He made an excellent recovery.

Case 3

This 9-year-old boy sustained a closed head injury after being thrown from a horse. He had an associated loss of consciousness that lasted approximately 10 minutes. En route to the hospital, his GCS score was 14. After arrival, his GCS score fluctuated between 13 and 14. His admission CT head scan demonstrated small amounts of subarachnoid hemorrhage and very small petechial hemorrhages over the right frontal and left temporal convexities. His neurological condition improved through the third hospital day. He then became mildly somnolent and had difficulty following verbal commands. A second CT scan demonstrated increased intraparenchymal swelling, near obliteration of cisterns, and more obvious petechial hemorrhages in the same frontal and temporal areas. He suffered a generalized seizure followed by bradycardia and respiratory arrest, and his Na level was 126. At the time of his clinical deterioration, he was noted to have an erythematous blotchy area on his chest, face, and limbs. An intraparenchymal ICP monitor was placed. ICP at insertion was 25 to 30 mm Hg, with later peaks of 60 to 80 mm Hg. The patient was treated aggressively to lower ICP and a 3-day pentobarbital coma was induced. His condition progressively improved and he made a good recovery despite ischemic damage to areas in the left basal ganglia.

Case 4

This 15-year-old boy presented with a history of nausea, vomiting, stiff neck, and fever of 104˚F. His medical history was significant for an endoscopic third ventriculostomy 3 months before presentation. Deterioration of his mental status during transport was reported. On arrival in the emergency department, his GCS score fluctuated between 8 and 10. He was noted to have a significant right otitis media and nuchal rigidity. He also had a pronounced erythematous macular rash that spread from his face to his chest, upper abdomen, and upper arms. This response was transient: it appeared when his obtundation seemed more severe and seemed to dissipate within 10 to 15 minutes, as he became more awake. He was admitted to the hospital and a lumbar puncture was performed; the opening pressure was in excess of 500 mm H2O ( > 37 mm Hg). His CSF cultures grew Streptococcus pneumoniae. He was treated with antibiotic drugs for 14 days, and a shunt was inserted when he complained of persistent mild headaches and his CT scan revealed progressive ventriculomegaly. His outcome was normal.

Case 5

This 13-year-old girl suffered an intraventricular hemorrhage while undergoing an endoscopic third ventriculostomy for treatment of L’Hermitte–Duclos disease. The hemorrhage was cleared with irrigation, and when she woke up she had no neurological deficits for approximately 2 hours, but then began to experience a severe headache. She was treated for postoperative headache with fentanyl (80 µg over 34 minutes, approximately 2.8 µg/kg/hour). She abruptly began to deteriorate neurologically, and had respiratory distress, bradycardia, and an erythematous flush affecting the left lower quadrant of her abdomen as well as her upper chest and arms. She was normothermic. A ventricular tap was performed and revealed an ICP in excess of 400 mm H2O ( > 30 mm Hg). After 15 to 20 ml of CSF was removed, she improved clinically and the flush disappeared. Further use of fentanyl did not provoke a flushing reaction. A head CT scan confirmed persistent intraventricular hemorrhage. She was treated with external ventricular drainage, and ultimately required placement of a permanent VP shunt; however, she went on to make a full recovery.

Discussion

The cases outlined in this paper share several salient features. All episodes were observed in a pediatric population. All patients were noted to have developed a flush-
these elevations were sudden and severe, lasting 5 to 15 minutes. Epidermal flushing occurred mainly in the chest, face, and upper limbs. Typically, the flush dissipated when ICP–lowering measures were instituted, and there was a corresponding clinical improvement. Only the patient in Case 3 had flushing in the absence of hydrocephalus.

Drugs cause peripheral vasodilation. The contribution of drugs as causes of flushing in the cases in this study was small. Most of these patients were in the initial phases of emergency treatment and few had received medications. The patient in Case 1 had received codeine for headache, and the one in Case 5 was recovering from general anesthesia and was treated with routine postoperative antibiotic and analgesic medications. Drugs or conditions known to cause flushing include: all the calcium channel blockers; ethanol; 2-phenylethylamine; quinidine; organic nitrates including nitroglycerin and amyl nitrite; bromocriptine; tricyclics; sildenafil; niacin; intravenously administered contrast media; adenosine 3,5-monophosphate; thyrotropin-releasing hormone; high-dose methylprednisolone; oral triamcinolone; cyclosporin; caffeine withdrawal; combination anesthesia of isoflurane and fentanyl; serotonin; cholinergic drugs such as metrifonate; many chemotherapeutic agents including doxorubicin, mitomycin, cisplatin, alpha-interferon, and dacarbazine; antiemetics including alizapride and metoclopramide; antibiotic agents including vancomycin and rifampin; and opiates.14

Local histamine injection in the skin produces the classic triple response, including transient flushing and wheal; the typical wheal (tissue edema at the site of maximal histamine concentration due to increased vascular permeability) was not observed in our patients (Table 1). In his definitive review of epidermal flushing disorders, Wilkin 14 noted that flushing is the result of transient vasodilation of the epidermal vasculature controlled by autonomic nerves and circulating vasoactive agents. Because autonomic nerves also control eccrine sweat glands, vasodilation mediated by autonomic nerves usually causes concomitant eccrine sweating. Agents that act directly on vascular smooth muscle without autonomic mediation cause flushing without increased sweating. Only the patient in Case 1 exhibited sweating before flushing, although it is possible that sweating occurred but was not observed in the other four children because of the urgency of their situation. If the flushing occurred without sweating, this would indicate that the flushing observed in our patients was not under the exclusive control of a normal autonomic system.

Autonomic functions are enormously complex and involve many more agents than the classic neurotransmitters acetylcholine and norepinephrine. The presence of peptides such as substance P, enkephalins, angiotensin, somatostatin, VIP, and nitric oxide at cholinergic ganglia indicates that these substances, in addition to classic neurotransmitters, are involved with a specific vasodilator function. The presence of these peptides in the skin vasculature suggests that these substances act as modulators of sympathetic regulation. Normally, regulation of the blood flow in skin resistance vessels is under sympathetic cholinergic control. At the ganglionic level the neuropeptides involved with a specific vasodilator function probably include acetylcholine and VIP, and differ from sudomotor specific cholinergic neurons in the paravertebral ganglia.

### TABLE 1
Clinical characteristics of five children with epidermal flushing and raised ICP*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Associated Findings</th>
<th>Site of Flushing (Duration)</th>
<th>Vital Signs</th>
<th>ICP (mm Hg)</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14, M</td>
<td></td>
<td>VP shunt malfunction</td>
<td>headache, brief periods of obtundation, emesis</td>
<td>trunk (10 mins)</td>
<td>BP 200/100 mm Hg, HR 98 bpm</td>
<td>unknown</td>
<td>VP shunt revision</td>
<td>poor</td>
</tr>
<tr>
<td>2</td>
<td>10, M</td>
<td></td>
<td>VP shunt malfunction</td>
<td>incoherence, nausea, 1st episode of flushing dissipated after hyperventilation w/mask; flushing recurred</td>
<td>face, chest, upper arms 2 × (several mins)</td>
<td>BP 150/102 mm Hg, HR 40 bpm</td>
<td>&gt;37</td>
<td>shunt revision</td>
<td>excellent</td>
</tr>
<tr>
<td>3</td>
<td>9, M</td>
<td></td>
<td>trauma, occipital fracture</td>
<td>limb, shivering at home, somnolent; increasing unresponsiveness 2 days posttrauma</td>
<td>chest, face, limbs (~10 mins)</td>
<td>BP 177/29 mm Hg, HR 132 bpm, temp 36°C, arrhythmias, Na 126</td>
<td>80, per ICP monitor</td>
<td>pantobital coma × 3 days</td>
<td>good; basal ganglia infarction, weakness in 1 leg</td>
</tr>
<tr>
<td>4</td>
<td>15, M</td>
<td></td>
<td>ventriculitis &amp; otitis, previous 3rd ventriculostomy; L'Hermitte–Durloc; bleeding during 3rd ventriculostomy</td>
<td>fever, emesis, obtundation en route to emergency room</td>
<td>face, chest, abdomen, arms (10–15 mins)</td>
<td>BP 141/71 mm Hg, HR 120 bpm, temp 37.5°C</td>
<td>&gt;37</td>
<td>antibiotic drugs × 14 days</td>
<td>excellent</td>
</tr>
<tr>
<td>5</td>
<td>13, F</td>
<td></td>
<td>L'Hermitte–Durloc; bleeding during 3rd ventriculostomy</td>
<td>headache, respiratory distress</td>
<td>arms, chest, lower limb abdomen (&lt;10 mins)</td>
<td>BP 80/60 mm Hg, HR 58 bpm, temp 36.3°C</td>
<td>&gt;30</td>
<td>VP shunt revision, external drain</td>
<td>excellent</td>
</tr>
</tbody>
</table>

*Temp = temperature.
which contain acetylcholine, VIP, and CGRP, substance P, and neurotensin, and are presynaptically modulated by enkephalin. Vasodilation occurs as a result of decreases in constrictor tone as well as local production of bradykinin in target sweat glands that are innervated by function-specific sudomotor fibers. Primary afferent collateral nerves that contain substance P, CGRP, and VIP make synaptic contacts with paravertebral neurons and thereby modulate their output. Finally, the hypothalamus and medulla together project abundant neuropeptide and monoamine-containing pathways to the intermediolateral cell column. The paraventricular nucleus of the hypothalamus has projections that contain vasopressin, oxytocin, metenkephalin, and substance P; the rostral medulla has pathways containing epinephrine, neuropeptide Y, and substance P; the raphe and ventromedial medulla contributes serotonin, substance P, enkephalin, somatostatin, and thyrotropin-releasing hormone.

The central pathophysiological basis for the epidermal flushing response in our group has not been determined, but intriguing possibilities exist that have been clinically tested. Among the central vasoactive neuropeptides, hCRH is released from the hypothalamus under a variety of stresses and induces synthesis and release of propiomelanocortin–derived peptides such as adenocorticotropin hormone, β-endorphin, and others from the pituitary gland. When injected intravenously in humans, hCRH produces not only facial flushing but also hyperventilation, with resultant CO2-dependent vasodistension of intracranial vessels and direct vasodilation of external carotid artery territory. Blood flow velocity in the territory of the external carotid artery increases more than 100% after intravenous injection of hCRH. Although this vascular effect is uniformly present with sufficient doses of hCRH, a visible flush may only be appreciated in up to 50% of humans studied. When injected into the ventricles of rats, CRH stimulates hippocampal acetylcholine and probably plays an important role in stress preparation, with very marked increases in arousal and cognition. Peripheral, CRH causes degranulation of skin mast cells when injected intradermally in rats; histamine, but not nitric oxide, is the main mediator of this effect.

Thermoregulatory flushing occurs naturally in hyperthermic patients who respond physiologically with heat-dissipating eccrine sweating and peripheral dilatation. The anterior hypothalamic region reacts to slight increases in the temperature of its arterial blood supply, and any derangement of the hypothalamus could impair temperature homeostasis. The patient in Case 5 suffered bleeding during a third ventriculostomy, and fluid was used to irrigate and clear the CSF; irrigation of the third ventricle would typically result in local hypothermia, and the homeostatic hypothalamic response would have normally been vasoconstrictive or heat-conserving. The observed single episode of flushing would not indicate a physiological response to temperature change. The deliberate surgical trauma to the hypothalamus by a third ventriculostomy may also have contributed to loss of its regulatory functions, but the flushing in this particular individual occurred more than 2 hours postsurgery, after an initially uneventful recovery. Elevation of ICP was the likely precipitating event in this individual case, although fentanyl had been given to treat the severe headache that preceded the flushing.

The neurosurgical literature abounds with case reports of central midline lesions associated with flushing reactions. Sustained flushing for 2 weeks was observed in one individual with glioblastoma diffusely infiltrating the optic chiasm and hypothalamus, thalamus, fornix, substantia nigra, and upper brainstem. Penfield’s classic and original description of diencephalic autonomic epilepsy is based on the single fatal case of a 41-year-old woman with a colloid cyst of the third ventricle and obstructive hydrocephalus who had headache, episodic syncopal attacks associated with flushing, hypertension, diaphoresis, pupil dilation, hiccup, Cheyne–Stoke respirations, incontinence, lacrimation, and shivering. According to Adams, et al.,” these attacks are thought to result from the removal of inhibitory influences on the hypothalamus, creating, in effect, a hypersensitive decorticated autonomic nervous system.”

Disturbances in the posterior fossa are infrequently associated with flushing. Autonomic instability was noted in a young man 8 months after partial resection of a hemangioblastoma arising in the area postrema, which had caused severe hydrocephalus. The patient experienced daily 30-minute episodes of hypertension, tachycardia, throbbing headache, and a “spreading, cape-like rash over his shoulders” extending over the nipples. Treatment of a large gastric ulcer and further resection of his tumor resolved the hypertensive episodes but the other features of his autonomic dysfunction persisted.

Finally, facial flushing is associated with irritation of the first division of the trigeminal nerve, causing the “trigeminal–lacrimal” vasodilatory reflex. In cats, the vascular response employs vasoactive intestinal polypeptide as its peripheral neurotransmitter. Part of the vascular response may be by antidiromic release of substance P and CGRP from trigeminal nerve terminals. Raynaud, et al., have reported that CGRP is a potent endogenous vasodilating agent in humans, with widespread distribution throughout the central nervous system, particularly in the trigeminal ganglion, the dorsal columns of the spinal cord, and periventricular diencephalic structures.

Conclusions

The transient flushing described in this paper occurred in a population of children who already had, in all cases, signs and symptoms of elevated ICP. In the clinical context of rapidly declining neurological function, the additional finding of transient epidermal flushing should alert the treating physician to the possibility of further precipitous neurological decline, and should serve as a red flag that prompts an appropriate response. Flushing probably occurs in less than 5% of children with acute elevations in ICP.

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References


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Address reprint requests to: Gregory W. Hornig, M.D., 5520 College Boulevard, Suite 425, Overland Park, Kansas 66211. email: gwhornig@mindspring.com.