Acute Stress-Induced Seizures and Loss of Consciousness in a Ten-Year-Old Boy With Cutaneous Mastocytosis

Editors:

Stress is known to exacerbate many conditions[1], including dermatoses[2], migraines[3], cardiovascular ischemia[4], and irritable bowel syndrome.[5] These conditions have a strong neuropsychological component and have been associated with mast cell activation. [6]

Case Report

A ten-year-old white boy presented (7/22/99) with acute headache, tonic-clonic seizures 2 to 3 minutes in duration, loss of consciousness, and urine and fecal incontinence, immediately following a confrontation concerning school performance. When admitted two hours later, the patient was conscious, but severely somnolent with conjunctival hyperemia, facial flushing, and peripheral cyanosis. Maculopapular, brownish cutaneous lesions (1–3 mm diameter) present on the neck, trunk, and upper and lower limbs (Fig. 1 A,B) had been diagnosed as urticaria pigmentosa (UP) when he was seven years old. He had previously presented with tonic clonic seizures (8/19/95). His vital signs were: HR 125/min, BP 80/40 mm Hg, O_2 saturation 77% and T=37.5°C. Laboratory values for this admission were: WBC 7400/mm^3, Ht 36.6%, Hb12.1 g/dl, platelets 265,000/mm^3, SGOT 24 U/l, SGPT 18.9 u/l, GT 42.5 U/l, alkaline phosphatase 333 U/l, K^+ 4.9 mEq/l, Na^+ 142 mEq/l, Ca^{++} 7.3 mg/dl, and random glucose 115 mg/dl. Total serum immunoglobulins, B and T leukocytes, EKG, cardiac echo and cardiac enzymes were normal. ESR was 17, antinuclear antibodies were negative, antibodies to smooth muscle fibers were weakly positive, and anti-cardiolipins were IgG 2 IU/ml, IgM 2.7 IU/ml. EEG showed well organized pattern with θ–α waves, 7/sec, slow without any focal or paroxysmal abnormalities.

The patient was first born vaginally at term (weight at birth 3.5 kg). Perinatal and family history were unremarkable (no seizures, immune, or psychiatric disorders). The patient had previously experienced seven episodes of loss of consciousness associated with headaches, facial flushing, peripheral cyanosis and hypotension; tonic-clonic seizures not associated with high fever were reported in four cases during the previous three years (7/12/96, 6/15/97, 9/10/97, 6/18/98). He often complained about abdominal pain with episodes of diarrhea alternating with constipation. All symptoms typically occurred under physical or psychological stress, such as exhaustive soccer or after school academic work. Previous studies included EKG, cardiac echo, EEG, MRI of the brain, and abdominal ultrasound (kidneys and ventricular aorta), as well as 24 hour urine catecholamines and vanillyl mandelic acid (VMA) to exclude pheochromocytoma, all normal. This child had been treated previously for seizures; first with sodium valproate (111.2 μg/ml) and later carbamazepine (9.8–10.4 μg/ml), without success, even though serum drug levels were therapeutic.

Biopsy of an UP lesion (Fig. 1B) was evaluated immunohistochemically and numerous tryptase-positive mast cells were noted. (Fig. 1 C,D) Most of these were degranulated (Fig. 1 E,F) with tryptase present extracellularly (Fig. 1 G–H). The initial value of total serum (Table 1) tryptase on admission (113 ng/ml) and the one upon discharge (32.9 ng/ml) were within the range (5–90 ng/ml) of adult systemic mastocytosis (SM) reported in adults.[7] Serum histamine on admission was also elevated (6.5 ng/ml) in line with that reported for SM.[7] SM was suspected, but bone marrow aspirate or biopsy was not performed due to lack of parental consent.

In the hospital, the patient was initially treated with intravenous normal saline, methylprednisolone, and 75 mg hydroxyzine hydrochloride, as well as 50 mg oral doxepin hydrochloride; he was discharged on 50 hydroxyzine and 5 mg doxepin qhs to limit the extent of daytime sedation.[8] Serum and histamine tryptase declined and were normal 24 months later (Table 1). Even though these values may represent variability over time, this patient has remained migraine and seizure free for more than 2 years. To the best of our knowledge, this is the only report of seizures precipitated by acute stress in a child with UP. "Vasomotor seizures" due to vascular collapse have been reported in adult SM patients.[9] An adult man with SM presented with loss of consciousness and fecal incontinence[10], while a female adult SM patient had recurrent episodes of headaches and syncope.[11] There have been only two reports of adult patients who experienced grand mal seizures, presumably because of cardiovascular collapse due to histamine release—one with SM[12] and the other with cutaneous mastocytosis.[13] In contrast, our patient presented with headaches and seizures, following acute emotional stress, without ever being severely hypotensive. Intracranial mast cells have been shown to have anatomical and functional associations with neurons and can be activated by acute stress in both the meninges[14] and the diencephalon.[15] Brain mast cell–derived mediators could, therefore, contribute to the headache and altered consciousness in this patient.

Mastocytosis is a heterogeneous group of conditions characterized by proliferation of mast cells in some tissues, most often the skin (UP), in which case it is usually benign. In 55% of cases, the onset of mastocytosis occurs before age two[16] and often presents with headaches and abdominal pain, sometimes called "abdominal migraines".[3] SM implies mast cell proliferation in the bone marrow and is increasingly identified by high serum tryptase.[7] A number of stem cell factor receptor (c-kit) mutations have recently been identified that may explain adult SM[17], but not childhood mastocytosis.[16] Mast cells originate in the bone marrow[18] and are distributed throughout the body, perivascularly and often close to neurons.[19] Clinical symptoms are variable and derive from mast cell vasoactive and proinflammatory molecules, released topically or systemically.[20] The

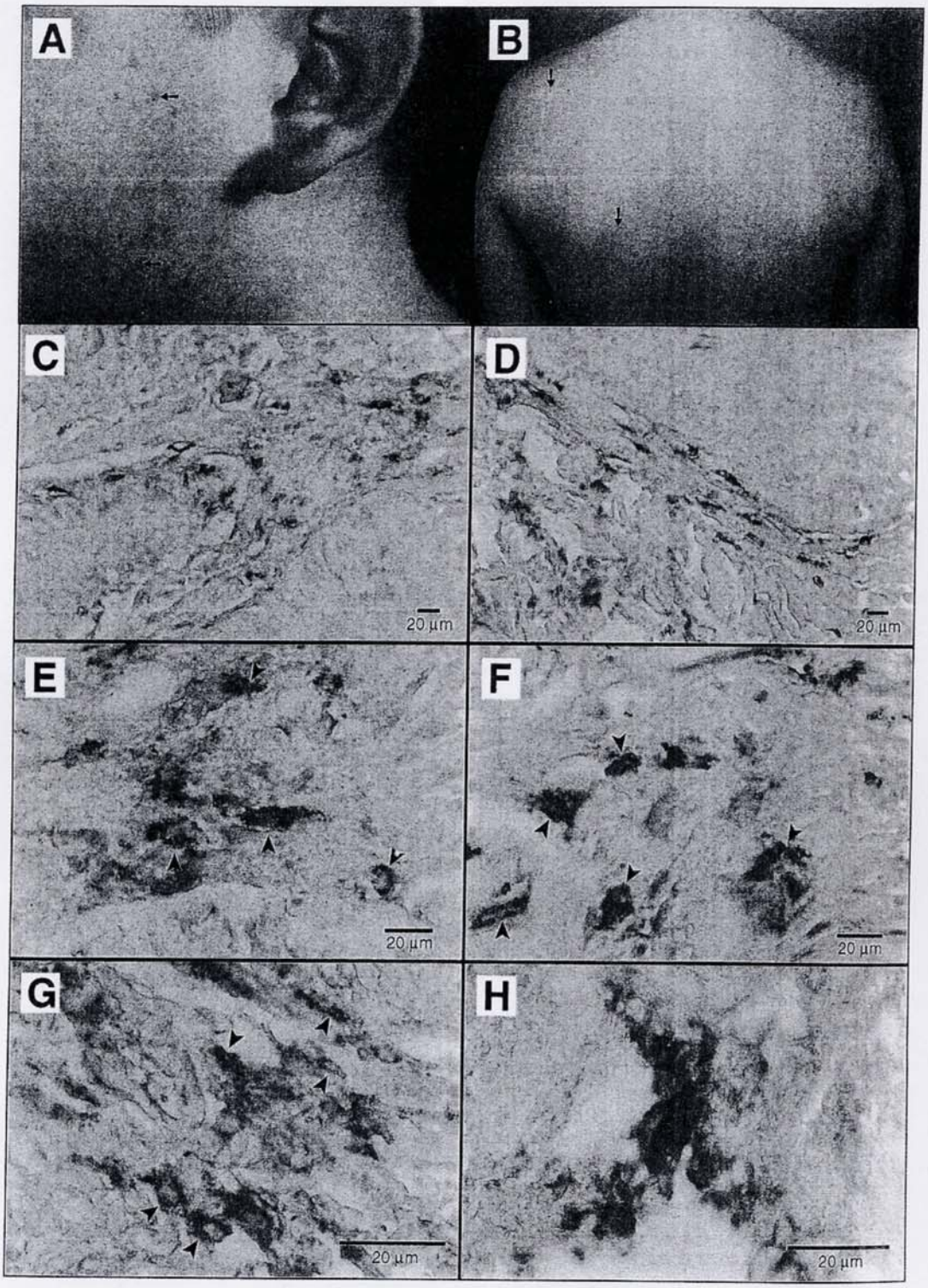

FIG. 1. Photographs of (**A**) facial and (**B**) shoulder areas showing UP lesions (dark arrows). Photomicrographs of a UP lesion from a punch biopsy, after ring infiltration with 1% lidocaine; (**C, D**) Note numerous mast cells staining red (arrowheads) immunohistochemically for tryptase (Chemicon International, Inc., Temecula, CA); (**E, F**) higher magnification to appreciate variable mast cell activation; (**G, H**) mast cell degranulation seen as (**G**) reduced staining or (**H**) extracellular tryptase. Scale Bar = 20 µm.

TABLE 1. Serum mast cell mediators

	Detection limit	Normal range	Admission (7/22/99)	After Tx (8/30/99)	After Tx (3/16/00)	After Tx (8/10/00)
Histamine	0.02 ng/ml	<1 ng/ml	11.1	6.5	ND	ND
Tryptase	0.5 ng/ml	<5 ng/ml	117	32.9	22.6	5.1

Histamine was measured by RIA (AMAC, Inc., Westbrook, ME) and tryptase with the automated fluoroenzymatic Unicap System (Kabi Pharmacia, Diagnostics, Inc., Piscway, NJ) which detects total (both α and β tryptase).

Tx, treatment; ND, not detectable.

main preformed mediators are histamine, proteases (chymase, tryptase) and proteoglycans (chondroitin sulfate, heparin). Newly synthesized mediators include prostaglandin D_2 (PGD_2), leukotriene C_4 (LTC_4), as well as many cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6).[18] Some molecules, such as histamine, can stimulate neurones directly.[21]

Treatment of mastocytosis aims to antagonize the biological actions of mast cell mediators, the triggers for which are not well understood.[22] Hydroxyzine and doxepin[23] were used in this case, both because they are histamine (H_1) and (H_1/H_2) receptor antagonists, respectively, with anxiolytic effects and they also partially inhibit mast cell activation.[24] It was also recommended that this patient refrain from food products or "cold" medications containing biogenic amines. Reduced homework and after-school work (strenuous sports) and avoidance of confrontations were instituted, whenever possible, to limit acute stress. Stress reduction by self-regulation was shown to decrease the incidence and severity of migraines and concomitant levels of urine tryptase in children.[3]

The multitude of mediators released from mast cells in different organs presents unique difficulties for diagnosis and treatment, especially in stress-induced condition (See accompanying editorial).

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Effects of Oral Procyclidine Administration on Cognitive Functions in Healthy Subjects: Implications for Schizophrenia

Editors:

It is widely accepted that cognitive impairment in schizophrenia, even that seen at the onset of illness, is not attributable to the use of conventional antipsychotic medication.[1,2] Medication with newer atypical antipsychotic drugs has been associated with normalization of a range of cognitive dysfunctions in schizophrenic patients.[2] Patients with schizophrenia are also often prescribed anticholinergics to counteract the extrapyramidal side effects caused by antipsychotics.[3] Anticholinergics have been shown to cause detrimental effects on cognitive functioning in normal and neurologically impaired human populations,[4,5] with particularly strong effects on memory[6] and attention.[7]

Procyclidine [1-cyclohexyl-1-phenyl-3- (pyrrolidin-1-yl)-propan-1-ol hydrochloride] is the most common anticholinergic drug used in the United Kingdom in patients with schizophrenia. No study has yet investigated its effects on cognitive functioning in normal or schizophrenic populations. We therefore examined the effects of two clinically relevant doses of procyclidine in healthy male subjects on a range of cognitive functions found to be impaired in patients with schizophrenia. It was hypothesized that procyclidine, especially at the higher dose, would disrupt cognitive functions in general, perhaps with stronger effects on tasks requiring memory and higher order cognitive processing.

Sixteen 19- to 45-year-old subjects participated in experiment 1 (10 mg of procyclidine or placebo), and 14 21- to 37-year-old healthy nonsmoking men (to reduce gender-related differences in performance) participated in experiment 2 (15 mg of procyclidine or placebo). All potential subjects were screened using the Structured Clinical Interview for DSM-IV Axis I Disorders–Research Version[8] and underwent semi-structured medical screening for thyroid dysfunction, glaucoma, heart disease, hypo- or hypertension, a history of severe mental illness, anorexia, violent or rapid mood changes, regular medical prescriptions, alcohol dependency, and drug abuse (ascertained by urine analysis) before being accepted as study participants.

Under double-blind conditions, subjects were randomly assigned in equal numbers and administered 10 mg of procyclidine and placebo orally on separate occasions at the same time of day 2 weeks apart in experiment 1 and 15 mg of procyclidine or placebo in experiment 2. A 3-mL sample was taken by venepuncture for gas-liquid chromatography analysis 2 hours after the administration of drug or placebo on each occasion. All subjects completed a comprehensive neuropsychological battery (listed in the footnote to Table 1) to assess memory, executive function, attention, and psychomotor speed 2 hours after the administration of drug or placebo. The testing was conducted after the 2-hour drug latency period so as to assess the maximum effect of procyclidine given orally.

The data from both experiments (separately) on various dependent measures were analyzed by mixed-model multivariate analysis of variance (Wilks' F), with drug condition as a within-subjects factor and drug order as a between-subjects factor. Significant effects were followed up with paired t-tests. All analyses were performed by SPSS for Windows version 8.0 (SPSS Inc., Chicago, IL). The alpha level for significant testing in all analyses was set at 0.05.

The mean plasma procyclidine concentration obtained after the administration of procyclidine for experiment 1 was 0.065 mg/mL (range: 0.02–0.10 mg/mL). The mean plasma procyclidine concentration for experiment 2 was 0.133 mg/mL (range: 0.06–0.22 mg/mL). For the placebo conditions, all plasma procyclidine concentrations were zero.

Both doses of procyclidine disrupted memory function as detected by the Buschke Selective Reminding Test[11] and the Wechsler Memory Scale–Revised.[12] The 15-mg dose but not the 10-mg dose caused decreased performance on the California Verbal Learning Test[13], the Wisconsin Card Sorting Test[14,16], and the Color-Word version of the Stroop test[19] . At neither dose did procyclidine significantly affect performance on the Letter Number Span test, the working memory[15] N-back task, the Continuous Performance test[17], the Finger Tapping test[20], or Trail Making A and B tests.[18,20]

The means and SDs for each cognitive test variable for experiment 2 under the drug and placebo conditions are presented in Table 1. This study demonstrates that a single administration of procyclidine has detrimental dose-dependent effects on a wide range of neuropsychological functions in normal subjects. These deficits seem to be dependent on dose (i.e., relatively stronger in experiment 2) and reversible, because they did not persist in the group that received a placebo on the second occasion. These findings are generally in agreement with those of previous studies for other anticholinergics. Cognitive processes underlying performance on the Buschke Selective Reminding Test seem to be most sensitive to the effects of procyclidine.[9]

These findings have important implications for the treatment and functional outcome of schizophrenia. The detrimental effects of procyclidine may even be stronger in patients with schizophrenia, because anticholinergics produce stronger effects in normal subjects with poor baseline performance and schizophrenic patients are known to exhibit