Recurrent attacks of vomiting, hypertension and psychotic depression: a syndrome of periodic catecholamine and prostaglandin discharge

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Abstract. A syndrome of periodic catecholamine and prostaglandin E2 discharge is described in 2 patients aged 17 and 3 years. They had recurrent attacks of vomiting, hypertension and psychotic depression for several years with a fixed periodicity. At initiation of the attack, plasma ACTH, AVP, norepinephrine and prostaglandin E2 were markedly elevated, whereas dopamine was undetectable. This resulted in hypercortisolemia, hyponatremia and oliguria, which were completely normalized when the attack subsided. Dopaminergic inhibition by metoclopramide injection induced a sustained rise in plasma bicyclo-prostaglandin E2 in the patients, a transient rise in 4 controls, and no response in 8 control children. The 4 control responders had significantly higher plasma norepinephrine levels and aldosterone responses than the non-responders (P < 0.001). There was a linear correlation between peak values of bicyclo-prostaglandin E2 and basal norepinephrine levels (r = 0.990, P < 0.001). The patients released bicyclo-prostaglandin E2 and aldosterone more easily than the control responders in terms of plasma norepinephrine and dopamine levels. Treatment of the patient with clonidine was partially effective, whereas administration of indomethacin completely suppressed recurrence of the attacks for 1 year. These results suggest the etiologic possibility that the patients have a decreased dopaminergic inhibition of prostaglandin E2-mediated norepinephrine secretion, which causes periodic discharge of norepinephrine and concomitant release of ACTH and AVP.

Recurrent abdominal pain and vomiting are common symptoms associated with a variety of disorders in childhood. Now the diagnosis of 'cyclic vomiting' has been eliminated from the standard textbook of pediatrics because it is regarded as a symptom of various underlying diseases rather than a clinical entity. However, we described previously a syndrome of severe vomitings, hypertension and psychotic depression without any definite lesion, which recurred periodically for several years (Sato et al. 1980, 1982). On the initiation of the attack, plasma ACTH and AVP were markedly elevated, resulting in hypercortisolemia, hyponatremia and hypo-osmolality in plasma. Urinary flow was diminished and oliguria was followed by polyuria at the end of the attack. Plasma norepinephrine (NE) was increased, which appeared to be the cause of hypertension. All these signs and laboratory abnormalities were completely absent during periods of remission. Since there had been no description of a similar disorder in the literature, we reported the patient as a syndrome of periodic ACTH and AVP discharge (Sato et al. 1982). As the cause of the syndrome we postulated periodic alteration of catecholamine (CA) in the central nervous system including the hypothalamus, because no other abnormality was found to explain the recurrent hypertension.
However, the exact mechanism remains to be elucidated.

It is clear that NE and dopamine (DA) play a transmitter role in the central nervous system. Studies on the iontophoretic administration of DA indicate that the predominant qualitative response is inhibiton of nerve cell function (Cooper et al. 1986). With regard to the regulation of CA release, prostaglandin E (PGE) is a potent inhibitor of NE release (Hedqvist 1977) and PGE-mediated feedback control of CA secretion has been postulated (Samuelson & Wennmalm 1971; Jungstad & Wennmalm 1973). It is difficult, however, to study the control mechanism in clinical materials because of the rapid degradation of PGE in the circulation (Granström et al. 1982). Recent technical advances have made it possible to measure the plasma concentration of PGE$_2$ after converting it to a stable metabolite, bicyclo-PGE$_2$ (cPGE$_2$) (Bothwell et al. 1982; Demers et al. 1983). This prompted us to examine the interrelation between PGE$_2$ and CA release in patients with this syndrome using a DA antagonist, metoclopramide (Plouin et al. 1976; Agabiti-Rosei et al. 1977). Another patient recently diagnosed was also included in the study.

### Subjects and Methods

Two girls aged 17 and 3 years with this syndrome were examined. Clinical data of the older patient (No. 1) were previously reported in detail (Sato et al. 1980). Clinical features and laboratory findings were very similar in both patients, and are summarized in Table 1. Patient No. 1 was admitted at the age of 9½ years because of recurrent attacks of vomiting and hypertension of 3 to 5 days’ duration during the previous 2 years. Her past history was not remarkable except a few episodes of vomiting. Since age 8 years, the frequency of attacks increased to 2 to 3 episodes per month. On the initiation of the attack, she was depressed, vomited continuously and complained of abdominal pain. Blood pressure was elevated to 170/110 mmHg and facial plethora was noted. Laboratory data during the attack showed elevated ACTH, AVP, cortisol, NE and glucose and decreased sodium in plasma (Table 1). Plasma

### Table 1.

Clinical features and laboratory data during attacks.

<table>
<thead>
<tr>
<th></th>
<th>Patient No. 1</th>
<th>Patient No. 2</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age and sex</strong></td>
<td>17 years, female</td>
<td>3½ years, female</td>
<td></td>
</tr>
<tr>
<td><strong>Age of onset</strong></td>
<td>7 years</td>
<td>2 years</td>
<td></td>
</tr>
<tr>
<td><strong>Periodicity of attacks</strong></td>
<td>10–14 days</td>
<td>3–4 weeks</td>
<td></td>
</tr>
<tr>
<td><strong>Duration of attack</strong></td>
<td>3–5 days</td>
<td>5–7 days</td>
<td></td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td></td>
<td>frequent</td>
<td>frequent</td>
</tr>
<tr>
<td>hypertension</td>
<td>160–170 mmHg</td>
<td>150–180 mmHg</td>
<td></td>
</tr>
<tr>
<td>psychotic depression</td>
<td>(+)</td>
<td>(+)</td>
<td></td>
</tr>
<tr>
<td><strong>Laboratory data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukocytosis and eosinopenia</td>
<td>(+)</td>
<td>(+)</td>
<td></td>
</tr>
<tr>
<td>Plasma Na (mmol/l)</td>
<td>131 ± 4 (14)</td>
<td>132 ± 1 (6)</td>
<td>134–146</td>
</tr>
<tr>
<td>K (mmol/l)</td>
<td>3.6 ± 0.5 (14)</td>
<td>4.1 ± 0.2 (6)</td>
<td>3.5–4.5</td>
</tr>
<tr>
<td>Blood glucose (mmol/l)</td>
<td>8.1 ± 0.4 (7)</td>
<td>6.1 ± 0.5 (3)</td>
<td>2.5–5.3</td>
</tr>
<tr>
<td>Ketonuria</td>
<td>(−/+)*</td>
<td>(−/+)*</td>
<td>(−)</td>
</tr>
<tr>
<td>ACTH (ng/l)</td>
<td>144 ± 74 (4)</td>
<td>150 ± 57 (5)</td>
<td>50</td>
</tr>
<tr>
<td>AVP (ng/l)</td>
<td>12.5</td>
<td>46.3 ± 23.9 (6)</td>
<td>1.5</td>
</tr>
<tr>
<td>Cortisol (nmol/l)</td>
<td>2200</td>
<td>1498 ± 94 (7)</td>
<td>82–413</td>
</tr>
<tr>
<td>Plasma renin (µg/l per h)</td>
<td>2.47, 3.13</td>
<td>1.0</td>
<td>6.7</td>
</tr>
<tr>
<td>Plasma aldosterone (nmol/l)</td>
<td>0.33, 0.37</td>
<td>0.19 ± 0.06 (9)</td>
<td>0.1–0.8</td>
</tr>
<tr>
<td>Urinary 17-OHCS (µmol/day)</td>
<td>59.6 ± 11.3 (6)</td>
<td>47.7 ± 9.3 (17)</td>
<td>2.8–15.5</td>
</tr>
<tr>
<td>17-KS (µmol/day)</td>
<td>6.9 ± 1.7 (6)</td>
<td>5.2 ± 0.6 (9)</td>
<td>7 (2–6 years)</td>
</tr>
</tbody>
</table>

*Values are mean ± SD. Number in parentheses: number of samples.

* Initially negative but positive as the attack progressed.
potassium remained at the lower limit of normal range. Urinary 17-OHCS was also increased. Urine volume was diminished during the episode, but followed by polyuria at the end of the attack, which subsided spontaneously and all symptoms returned to normal. During 10 weeks of hospitalization, 8 episodes were observed. She had a normal skull radiography, ocular fundus, CT scanning of the brain, whole-body scanning, iv pyelography, 131I-Hippuran renography, and EEG, except for a slight increase in 75Se-cholesterol uptake in both adrenal glands. She was treated with a daily dose of 100–120 mg of chlorpromazine, which reduced frequency of the episodes to 2–3 times per year. From July 1983, 0.075 mg of clonidine was administered twice a day, which eliminated the attack for 2 years. The medication was stopped in December 1985. After 6 months, the episodes recurred. The clonidine treatment was started again, but this time it was not effective; short attacks lasting 1–2 days recurred weekly. For re-evaluation of the disorder, she was admitted to Kanazawa University Hospital.

In patient No. 2, onset of vomiting with hypertension and psychotic depression was at 2 years of age. No appreciable cause was found. The episodes lasted for 5–7 days and recurred at 3–4 weeks intervals. No causative lesion was revealed at extensive clinical and laboratory examinations, including gastrointestinal X-ray, CT scanning of the brain, adrenal glands and abdomen, 171I-metaiodobenzyl guanidine scanning of the adrenal glands, EEG, and biochemical blood analyses. Endocrine data are listed in Table I. The possibility of a phaeochromocytoma was excluded by the normal excretion of CA and its metabolite during symptom-free periods and a normal scintigram of the adrenal glands. Liddle’s syndrome was also unlikely because of the absence of hypokalemia. Treatment with 0.075 mg of clonidine and 0.3 mg of reserpine daily modified the periodicity of the attacks but did not eliminate the symptoms.

To elucidate the cause of the disorder, serial determinations of plasma and urinary CA were made during the episodes and intermittent phases. Fractionated urine samples were obtained during the attacks, whereas 24-h specimens were used in attack-free periods. Urine was acidified by the addition of 1 ml of 6 mol/l HCl per 100 ml and stored at −20°C until assay.

In an attempt to study the inhibitory effect of endogenous DA on NE and epinephrine (E) secretion, 0.5 g of L-dihydroxyphenylalanine (L-DOPA) was administered orally to 5 adult volunteers before sleep and urine samples were collected the next morning. The effect of a bolus of 0.22 mg clonidine on CA excretion was also examined. Control urine samples were collected in the same subjects without medication. The tests were repeated 2–3 times.

The effect of dopaminergic inhibition by metoclopramide, a DA antagonist, on plasma CA and aldosterone was studied in the patients and 12 children aged 2–15 years. A bolus of 0.3 mg/kg metoclopramide was injected iv. Heparinized blood samples were obtained at 0, 15, 30 and 45 min. Plasma was immediately separated by centrifugation at 4°C and stored at −20°C until assay.

Plasma and urinary CA concentrations were determined by high-performance liquid chromatography (Shimadzu LC-5A, Kyoto, Japan) with an electrochemical detector (Coulochem 5100A, ESA Inc, USA). The sensitivity of the method was 50 pmol/l of CA. The intra-assay coefficient of variance was within 5%. The recovery of CA absorbed to activated alumina was 60–70% calculated from the added standard, dihydroxybenzylamine. Urinary CA excretion rate was expressed in nmol/h. Plasma aldosterone was measured by RIA with commercially available kit (ALDOC TK-100, CIS, Sorin Biomedica, France).

Plasma cPGE2 levels were determined by RIA using cPGE2-matched component (New England Nuclear, Dupon, USA). Before assay, 0.5 ml of plasma was pre-incubated with 30 µl of 1 mol/l NaOH for 24 h at 37°C. This converted plasma PGE2 into a stable metabolite, cPGE2 (Fitzpatrick et al. 1980). After incubation, pH was neutralized with 70 µl of 1 mol/l KH2PO4. Assay buffer consisted of 0.01 mol/l phosphate buffer (pH 7.4) containing 0.9% NaCl, 5 mmol/l EDTA, 0.1% gelatin and 0.01% ethylmercuricacilayte (Thimerosal®, Sigma). [5,6,11,12-H]bicyclo PGE2 (70 Ci/mmol) was reconstituted with 1.0 ml of distilled water (1.0 mCi/ml) and diluted to 10 ml with the assay buffer. Serial concentrations of standard cPGE2 from 0.1–10 nmol/l were prepared with the assay buffer containing 4% bovine serum albumin. The mixture of 100 µl of plasma or standard solution, 100 µl of [3H]bicyclo-PGE2 and 100 µl of anti-bicyclo-PGE2 antibody was incubated for 16–24 h at 4°C. Free and bound cPGE2 were separated by addition of 1.0 ml of 1% dextran-coated charcoal in the assay buffer without gelatin. After centrifugation at 3000 rpm for 15 min at 4°C, the radioactivity of the supernatant was counted with a liquid scintillation spectrophotometer. All samples were assayed in duplicate. The sensitivity of the assay was 10 fmoles and the intra-assay coefficient of variance was 4 ± 3% (SD) (N = 20). The plasma dilution curve paralleled well the standard curve. The plasma cPGE2 concentration in 15 normal children was 48 ±14 pmol/l ranging from undetectable level to 83 pmol/l. Statistical analysis was performed using the Student’s unpaired t-test.

Results

Urinary CA excretion in the patients

Urinary excretion rates of NE and DA in patient No. 1 were markedly increased during the attacks
but that of E remained at a low level (Fig. 1). Urinary flow was diminished during the episode and abruptly increased at the end of the attack. Parallel fluctuation of DA excretion and urine flow was also observed in symptom-free intervals, which was stabilized after the administration of indomethacin. In patient No. 2, concomitant increases in NE, E and DA excretion were noted during the attacks (Fig. 2).

**Changes in plasma CA and cPGE₂ in the patients**

In accordance with the changes in urinary CA excretion, plasma NE levels in patient No. 1 gradually increased during the attack and fell rapidly...
at the end (Fig. 3). In contrast, plasma DA was undetectable during the attack and rose to normal range in attack-free periods, whereas plasma E was undetectable throughout the observation period. This secretory profile of CA is quite different from that in usual stress reactions. Patient No. 2 also showed a similar change in plasma NE and DA, but E was elevated during the episode (Fig. 4). In both patients, plasma cPGE₂ levels were abnormally high during the attack, to decrease promptly to the normal range at the end of the attack (Figs. 3 and 4). cPGE₂ tended to rise episodically in patient No. 1, but was completely suppressed after indomethacin administration (Fig. 3).

**Effect of L-DOPA on NE and E secretion**

Since plasma DA was undetectable during the episodes in both patients, the effect of endogenous DA on NE and E secretion was examined in control subjects. Administration of L-DOPA, which is endogenously metabolized to DA, significantly suppressed urinary NE and E excretion ($P < 0.01 - 0.001$ vs control) (Table 2). This suggests the existence of a feedback inhibition by DA of NE and E secretion. Clonidine, a specific $\alpha_2$-receptor agonist, also showed a marked inhibition of urinary NE and E as well as DA excretion.
Table 2.
Effect of L-DOPA or clonidine administration on urinary excretion of catecholamines in control subjects.

<table>
<thead>
<tr>
<th>Medication</th>
<th>No.</th>
<th>Norepinephrine (µmol/mmol creatinine)</th>
<th>Epinephrine (µmol/mmol creatinine)</th>
<th>Dopamine (µmol/mmol creatinine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-free</td>
<td>14</td>
<td>1291 ± 661</td>
<td>156 ± 128</td>
<td>13.1 ± 4.0</td>
</tr>
<tr>
<td>L-DOPA</td>
<td>14</td>
<td>56 ± 43**</td>
<td>44 ± 37*</td>
<td>32.7 ± 35.6</td>
</tr>
<tr>
<td>Clonidine</td>
<td>10</td>
<td>34 ± 25**</td>
<td>3 ± 5*</td>
<td>1.0 ± 0.2**</td>
</tr>
</tbody>
</table>

L-DOPA (0.5 g) or clonidine (0.225 mg) was administered orally before sleep and urinary catecholamines were measured on the next morning.

* P < 0.01, **P < 0.001 vs drug-free values. Values are mean ± SEM.

Effect of DA inhibition on plasma cPGE2
Both patients had elevated cPGE2 levels which were closely associated with the clinical episode. Therefore, the effect of DA inhibition on plasma cPGE2 concentration was studied by iv injection of metoclopramide in the patients and 12 control children. After metoclopramide administration, plasma cPGE2 was increased in the 2 patients and 4 controls, whereas the others did not respond to the inhibition (Fig. 5). The cause of the different responsiveness of the control children was analyzed in terms of plasma CA levels (Fig. 6). The responders had definitely higher NE than the non-responders (P < 0.001). E and DA were not significantly different, although E tended to be elevated in the responders. This indicates that the responders had a relatively high sympathetic activity and that when the dopaminergic tone is suppressed, PGE2 is released into circulation. Indeed, there was a linear correlation between cPGE2 peak and basal NE level in the responders (r = 0.990, P < 0.001) (Fig. 7). cPGE2 appears to be released at a plasma NE level above 2.4 nmol/l in control subjects. In contrast, the patients had a lower NE and DA threshold for PGE2 release. This is probably because they have decreased dopaminergic tone even in attack-free periods, which is demonstrated in plasma aldosterone after metoclopramide administration (Fig. 8). The responders showed higher aldosterone levels than the non-responders, whereas that of patient No. 2 was markedly exaggerated: the peak value exceeded 4.2 nmol/l.

Therapeutic effect of clonidine and indomethacin
Administration of a daily dose of 0.15 mg of clonidine to patient No. 1 suppressed recurrence of the attacks for 2 years. However, the second treatment with the drug after relapse was not so effective, although the symptoms were less severe and the duration was shorter. Combined therapy with clonidine and reserpine to patient No. 2 was also unsatisfactory. However, abrupt cessation of the medication provoked a typical attack, indicating the involvement of the noradrenergic mechanism in this disorder. In contrast, indomethacin administration to patient No. 1 at a dose of 100 mg/day inhibited recurrence of the episodes as well as fluctuation of DA excretion for an observation period of 1 year.
Plasma CA responses to 0.3 mg/kg MCP in 12 control patients. (●), cPGE₂ responder (N = 4); (○), cPGE₂ non-responders (N = 8). Values are mean ± SEM. *P < 0.01, **P < 0.001 vs non-responders.

Correlation between plasma cPGE₂ after MCP loading and basal NE (upper panel) or basal DA (lower panel). (▲), patients; (●), cPGE₂ responders among controls; (○), non-responders among controls. Dotted area: lower limit of sensitivity in the cPGE₂ assay. There was a linear correlation between peak cPGE₂ and basal NE above 2.4 nmol/l (r = 0.990, P < 0.001).

Plasma aldosterone responses to 0.3 mg/kg MCP. (▲), patient No. 2; (●), cPGE₂ responders (N = 4); (○), cPGE₂ non-responders (N = 8). Values are mean ± SEM. *P < 0.01, **P < 0.001 vs non-responders.
Discussion

We demonstrate that the 2 patients with 'periodic ACTH and AVP discharge' had episodic CA release during the recurrent attacks. Since no other causative abnormality was found in the patients, the hypertension is reasonably ascribed to the elevated NE. The increased CA release cannot be regarded as a secondary reaction to the stress of vomiting, but is closely associated with the cause of the disorder. The reasons are as follows: a) Plasma E in patient No. 1 was not detectable throughout the episode; this is an unusual CA profile in a stress reaction. b) Urinary DA fluctuated highly even in the attack-free period; in our experience, urinary DA remains at a relatively stable level even in vomiting associated with gastrointestinal disorders. c) The regular periodicity of the attacks and the duration of 10 years cannot be explained by a usual stress reaction. d) Abrupt stopping of clonidine in patient No. 2 provoked the typical clinical manifestations. A CA secreting tumour is also unlikely as the cause of the disorder, because a) the magnitude of NE release was within the range of the physiological stress reaction and plasma DA was undetectable; b) the CA excretion was normal during the intermittent phase; c) adrenal scintigraphy and CT scanning were negative, and d) associated ACTH and AVP release together with psychotic depression indicated central nervous system origin. However, we do not consider that NE release is the primary cause, but an alteration in the regulatory mechanism of NE secretion must be involved, since the initial NE surge was not so high and NE rose gradually as the attack progressed.

Much evidence is accumulating suggesting that endogenous humoral factors such as prostaglandins, vasoactive amines and opioid peptides may regulate CA release by a direct local action on adrenergic nerve terminals. Prostaglandins of E series are potent inhibitors of neuronally-induced release of NE (Fredholm & Hedqvist 1975; Hillier & Templeton 1980; Reimann et al. 1981). On the contrary, PGE2 is reported to enhance selectively NE release in the brain (Roberts & Hillier 1976). When administered into the ventricle, it stimulates NE, ACTH, AVP and growth hormone release, producing a rise in the plasma levels of these hormones (Feuerstein et al. 1982; Vilhardt & Hedqvist 1970). Elevation of blood pressure and heart rate, and antidiuretic effect are also reported (Leksell 1976; Hoffman & Schmid 1979). These actions of PGE2 afford a reasonable explanation for the clinical symptoms and endocrine abnormalities of the syndrome. Indeed, plasma cPGE2 levels were increased prior to the rise in NE and abruptly declined at the end of the attack. However, this might not necessarily be specific for the disorder because of the wide tissue distribution of PGE2.

The inhibitory action of DA in the central nervous system and the undetectable plasma DA during the episode led us to the assumption that a decreased dopaminergic tone is the more important causative factor in the disorder. Therefore, we examined at first the effect of endogenous DA on NE secretion, and secondly the effect of dopaminergic inhibition by metoclopramide on cPGE2, CA and aldosterone in plasma. Actually, DA derived from L-DOPA suppressed NE and E secretion in normal controls (Table 2). Administration of metoclopramide induced cPGE2 release, which was dependent on plasma NE levels. The counterbalance between NE and DA appears to be important for PGE2 release.

The cPGE2 responses to metoclopramide varied considerably in normal control children. This is in part due to individual variation of the sympathetic activity, but also to age-related changes in dopaminergic tone, which increases progressively with age (study in progress). To match the ages of the patients, control children aged 2–15 years were selected, which might have caused the variation of cPGE2 responsiveness. Even in consideration of this age-related variation, the patients was hypersusceptible to dopaminergic inhibition and showed a low threshold for PGE2 release. An exaggerated response of aldosterone to metoclopramide also supports their decreased tone of the inhibitory dopaminergic mechanism, since aldosterone is known to be under the control of dopaminergic inhibition (Carey et al. 1980). Furthermore, the therapeutic efficacy of indomethacin rather than clonidine supports the concept that PGE2 release by diminished dopaminergic tone is most crucial as the cause of the disorder than NE release.

In conclusion, we reported 2 patients with a syndrome of periodic CA and PGE2 discharge having the clinical features of recurrent vomittings, hypertension and psychotic depression. The syndrome appears to be due to a decreased dopaminergic inhibitory mechanism in the central
nervous system, which causes periodic discharge of NE, ACTH and AVP. Since we reported the syndrome in 1980 and 1982, a number of similar cases has been accumulated at the annual meetings of the Japan Paediatric Endocrine Society. We believe that this syndrome is not rare in childhood and exists as a distinct clinical entity with definite endocrine abnormalities, although many problems remain to be elucidated, especially as to etiology, therapy and natural outcome.

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References


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