Fever of unexplained origin, biochemical Cushing’s disease and cerebral dysrhythmia corrected by valproate sodium

José M. López-Moreno, MD, FACP
José A. Rodríguez-Portales, MD
Daniel Mahana, MD

A patient with cerebral dysrhythmia and fever of unexplained origin for 2 years is described. She had elevated and nonsuppressible levels of urinary 17-hydroxycorticosteroids but no clinical features of hypercortisolism. Treatment with valproate sodium corrected all the abnormalities. It is postulated that cerebral dysrhythmia can affect the hypothalamic mechanisms of body temperature and regulation of adrenocorticotropic hormone levels.

Une malade a présenté depuis 2 ans une dysrythmie cérébrale et une fièvre d’origine inconnue. Malgré l’absence de signes cliniques d’hypercortisolie, elle montre une excrétion urinaire excessive de 17-hydroxycorticostéroïdes réfractaire à la suppression. Le traitement par le valproate de sodium rectifie toutes ces anomalies. On émet l’hypothèse que la dysrythmie cérébrale pourrait affecter les mécanismes hypothalamiques de régulation de la température et de la sécrétion d’adrénocorticotropine.

The association of cerebral dysrhythmia and fever has not been reported in the absence of diseases or drugs known to cause fever. Cerebral dysrhythmia, however, can be associated with paroxysmal increases in urinary 17-hydroxycorticosteroid (17-OHcs) levels.1 We describe a patient with chronic fever and electroencephalographic evidence of cerebral dysrhythmia who also met the diagnostic criteria for Cushing’s disease. Treatment with valproate sodium corrected the dysrhythmia and fever and restored the normal suppressibility of the pituitary–adrenal axis by dexamethasone.

Case report

A 20-year-old white woman was admitted to hospital because of severe throbbing headache for 5 years and well tolerated, almost daily, but irregular, episodes of fever (temperature 37.2°C to 38.5°C) for 2 years. She had consulted many physicians, who had treated her with various analgesic and antipyretic medications.

She was a high school secretary. She had no history of head trauma, seizures or unconsciousness. Her menses were regular. During the previous year she had gained 10 kg of body weight and her blood pressure had increased from 130/70 to 160/90 mm Hg. She had experienced no polypuria, polydipsia or polyphagia.

At the time of admission her axillary temperature was 37.8°C and her blood pressure 160/90 mm Hg. Her height was 172 cm and her weight 67 kg.

The blood leukocyte count was 6.0 X 10^9/L (59% segmented neutrophils, 36% lymphocytes and 5% monocytes) and the hematocrit 40%. The platelet count was normal. The erythrocyte sedimentation rate was 10 mm/h. The urine sediment contained one leukocyte and two erythrocytes per high power field. Serum chemical determinations revealed the following levels: albumin 42 g/L, alkaline phosphatase 30 U/L, aspartate aminotransferase 22 U/L and lactate dehydrogenase 118 U/L. Antinuclear antibodies, hepatitis B surface antigen and LE cells were not detectable in the serum. A serologic test for syphilis yielded negative results, as did tests for toxoplasmosis, brucellosis and salmonellosis.

There was no reaction to an intradermal injection of 2 units of purified protein derivative. Cultures of blood and urine specimens yielded no microorganisms, and no pathogens could be cultured from throat swab specimens. No infectious foci were found in the mouth.

A liver biopsy specimen was normal. Intravenous pyelograms, chest and skull x-ray films and computed tomography (CT) scans of the abdomen were normal. An exploratory laparotomy did not reveal any abnormality. Two lumbar punctures revealed normal cerebrospinal fluid; no microorganisms, including acid-fast bacilli, could be cultured. Carotid angiograms and three CT scans of the brain showed no abnormalities, and repeated examination of the visual fields gave normal results.

Electroencephalograms (EEGs) showed widespread dysrhythmia, more evident in the deep midline structures but without focalization.

Urinary 17-OHcs levels were determined by the method of Silber and Porter,2 and serum cortisol, adrenocorticotropic hormone (ACTH) and urinary free cortisol levels were determined by specific radioimmunoassays (Nicholls Laboratories, Los Angeles). A suppression test with 2 and 4 mg/d of dexamethasone was done as described by Liddle.3 Six doses of metyrapone, 750 mg every 4 hours, were given, and the 24-hour urinary 17-OHcs levels were determined on the day before and the day after the metyrapone was given.

The results of biochemical analysis were consistent with those of Cushing’s disease: an increased 24-hour urinary 17-OHcs level (which was decreased by the administration of 8 but not 2 mg/d of dexamethasone), a high urinary free cortisol level and a good response of the ACTH level to the administration of metyrapone (Table I). The 24-hour urinary pregnanediol level during the luteal phase was 3.7 mg (11.5 μmol); the normal 24-hour level during the ovulatory cycle is greater than 2.5 mg (7.8 μmol).
Plasma concentrations of human growth hormone, thyroid-stimulating hormone, triiodothyronine, thyroxine and prolactin were determined by radioimmunoassay. The results of stimulation with thyrotropin-releasing hormone (Relefact TRH, Hoechst Canada Inc.), 200 μg administered intravenously, are shown in Table II. Hypoglycemia was induced with 0.15 units of regular insulin per kilogram of body weight administered intravenously; the results are shown in Table III.

The patient was treated with phenytoin, 300 mg/d for 3 months, but there was no change in her EEG pattern or her symptoms. After discontinuation of phenytoin, valproate sodium, 750 mg/d, was given. There was progressive resolution of her symptoms, including the fever and biochemical hypercortisolism, and of the dysrhythmia (Fig. 1). Complete remission was achieved within 4 months after the start of therapy. At the time of writing she has been taking valproate sodium for 3 years and continues to be asymptomatic.

Discussion

Our patient’s condition was characterized by chronic fever of undetermined origin, headache, and biochemical findings suggestive of Cushing’s disease. There were no clinical stigmata of hypercortisolism. The episodes of fever were irregular and were not accompanied by a febrile syndrome; their origin remained unexplained in spite of extensive investigation. Treatment of the cerebral dysrhythmia with valproate sodium resulted in complete remission of the fever and headache, normalization of the EEG pattern and improvement of the pituitary—adrenal function.

There has been only one report of a patient with hypercortisolism and paroxysmal cerebral dysrhythmia that involved hypothalamic structures. In this patient both the fever and the increment of 17-OHcs excretion, which was not suppressed by the administration of dexamethasone, were paroxysmal. In our patient the presence of generalized dysrhythmia suggests that epilepsy may in some way have interfered with normal hypothalamic function. This deleterious effect could have been expressed by abnormal regulation of body temperature and abnormal hypothalamic control of the pituitary—adrenal axis.

The hypercortisolism did not have an anatomic pituitary substrate, as evidenced by the results of repeated cerebral CT scans. Other functional pituitary disturbances were not detected, as shown by the patient’s response to stimulation with thyrotropin-releasing hormone and insu-

**Table I—Results of hypothalamic—pituitary—adrenal axis studies in a patient with cerebral dysrhythmia**

<table>
<thead>
<tr>
<th>Date</th>
<th>Condition</th>
<th>Serum Cortisol, μg/dl (nmol/L)</th>
<th>ACTH,* pg/mL (pmol/L)</th>
<th>Free cortisol, μg/24 h (nmol/24 h)</th>
<th>17-OHcs,† mg/24 h (μmol/24 h)</th>
<th>Creatinine, g/24 h (mmol/24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td></td>
<td>9 am: 7–25 (193.3–689.7)</td>
<td>20–100 (4–22)</td>
<td>&lt;200 (551.8)</td>
<td>2.9–6.3 (8.0–17.4)</td>
<td>0.8–2.0 (7.1–17.7)</td>
</tr>
<tr>
<td>April 1978</td>
<td>Basal</td>
<td>4 pm: 50%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>May 1978</td>
<td>Basal</td>
<td>9 am: 18.0 (496.6)</td>
<td></td>
<td></td>
<td>10.2 (28.1)</td>
<td>1.1 (9.7)</td>
</tr>
<tr>
<td>October 1978</td>
<td>Basal</td>
<td>4 pm: 34.0 (938.1)</td>
<td></td>
<td></td>
<td>11.8 (14.6)</td>
<td>1.2 (10.6)</td>
</tr>
<tr>
<td></td>
<td>Second day of therapy with dexamethasone, 2 mg/d</td>
<td></td>
<td></td>
<td></td>
<td>6.5 (17.9)</td>
<td>1.2 (10.6)</td>
</tr>
<tr>
<td>January 1979</td>
<td>Basal (Day after metyrapone therapy)</td>
<td></td>
<td></td>
<td></td>
<td>2.1 (5.8)</td>
<td>1.1 (9.7)</td>
</tr>
<tr>
<td>October 1980</td>
<td>Basal (after 1 year of valproate therapy)</td>
<td>9 am: 25.0 (689.8)</td>
<td></td>
<td>276 (761.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Second day of therapy with dexamethasone, 2 mg/d</td>
<td></td>
<td></td>
<td>20.2 (55.7)</td>
<td>1.2 (10.6)</td>
<td></td>
</tr>
</tbody>
</table>

*ACTH = adrenocorticotropic hormone.
†17-OHcs = 17-hydroxy corticosteroids.
lin. Also, the presence of normal and ovulatory cycles attests to the normalcy of her gonadotropic function.

The mild basal hyperprolactinemia that hyper-responded to thyrotropin-releasing hormone may have caused a decrease in hypothalamic prolactin inhibitory factor. The fact that valproate sodium corrected the EEG abnormalities and was coincident with the disappearance of fever and an improvement in adrenal ACTH-dependent function makes it tempting to postulate an etiologic relation at the hypothalamic level.

Valproate sodium is an antiepileptic drug that increases the γ-aminobutyric acid (GABA) level in the central nervous system through stimulation of the enzyme glutamic decarboxylase or by inhibiting the degradation of GABA. GABA has been found in the brain, the hypothalamus and the pituitary gland in humans and animals. In mice GABA acts as a potent inhibitor of corticotropin-releasing hormone. Treatment with valproate sodium has recently been reported as effective for ACTH and pro-opiomelanocortin hypersecretion in Nelson's syndrome.

Since cerebral dysrhythmia has been reported to be associated with an excess of endogenous glucocorticoid and since valproate sodium does not appear to affect the regulation of body temperature and cortisol metabolism, it seems that the improvement in our patient resulted from the effect of valproate sodium on the cerebral dysrhythmia. However, she still had slightly elevated urinary free cortisol levels after 1 year of treatment in spite of a complete clinical remission.

The possibility that this antiepileptic agent was effective only in the treatment of the dysrhythmia and that the remission of the hypercortisolism corresponded to that spontaneously seen in Cushing's disease cannot be disregarded, but it seems unlikely. Discontinuation of valproate sodium therapy seemed unethical at the time of writing.

Although our patient met the classic biochemical criteria for Cushing's disease, the following facts continue to intrigue us: the response of the urinary 17-Ohcs level to metyrapone therapy was inadequate to be compatible either with a normal pituitary–adrenal axis or with Cushing's disease, and there was a rapid response of the growth hormone level to induced hypoglycemia, an unusual finding in Cushing's disease. It may be that these findings are compatible with a hypothalamic disorder that only partially deranges pituitary ACTH secretion.

Our case illustrates the complexity of hypothalamic and suprathyroidal influences on ACTH regulation. Epilepsy should be considered as a cause of prolonged fever.

References


Table II—Results of stimulation with thyrotropin-releasing hormone, 200 µg administered intravenously

<table>
<thead>
<tr>
<th>Variable</th>
<th>Condition: level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
</tr>
<tr>
<td>Plasma thyroid stimulating hormone, mU/mL</td>
<td>0.5</td>
</tr>
<tr>
<td>Plasma triiodothyronine, ng/dL (nmol/L)</td>
<td>90 (1.4)</td>
</tr>
<tr>
<td>Plasma thyroxine, µg/dL (nmol/L)</td>
<td>9.1 (117.1)</td>
</tr>
<tr>
<td>Plasma prolactin, µg/L</td>
<td>25.0</td>
</tr>
</tbody>
</table>

Table III—Results of induction of hypoglycemia with 0.15 units of regular insulin per kilogram of body weight administered intravenously

<table>
<thead>
<tr>
<th>Variable</th>
<th>Condition: level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
</tr>
<tr>
<td>Serum glucose, mg/dl (mmol/L)</td>
<td>129 (7.2)</td>
</tr>
<tr>
<td>Plasma human growth hormone, µg/L</td>
<td>3.9</td>
</tr>
<tr>
<td>Serum cortisol, µg/dL (nmol/L)</td>
<td>21.7 (598.7)</td>
</tr>
</tbody>
</table>

Fig. 1—Electroencephalographic pattern before (left) and during (right) valproate sodium treatment. Note resolution of widespread dysrythmia.
Prescribing Information

ACTION

Vibramycin is a broad spectrum antibiotic and is active against a wide range of gram-negative and gram-positive organisms. Vibramycin exerts its antibacterial effect by inhibition of protein synthesis. It is difficult to suggest that oral Vibramycin, because of its rapid and almost complete absorption, may have less effect on the gut flora than other tetracyclines. Hinton (1968) has reported that the normal dosage regimen of tetracycline HCl administered to 17 volunteers was associated with important effects on the intestinal flora in terms of both changes in total population and the emergence of resistant strains. Large doses of oral Vibramycin (double the maximum recommended dosage) had to be administered to produce an equivalent effect. In a similar number of volunteers, however, administration of the normal dosage regimen of oral Vibramycin was associated with substantial changes effect on flora. Baruma (1968) noted that the gut flora of patients on various dosages of oral Vibramycin for 10-80 days showed no significant deviation from the normal flora in the flora of a control group of patients. These data suggest that microbiological intestinal complications (e.g., diarrhea) associated with tetracycline therapy may be less frequent when ordinary therapeutic doses of doxycycline are used.

INDICATIONS AND CLINICAL USE

Oral Vibramycin is indicated for the treatment of respiratory infections such as single and multiple pneumonia, broncho-pneumonia, bronchitis, sinusitis, pharyngitis, tonsillitis, and others. Vibramycin is also recommended for the treatment of upper respiratory tract infections (e.g., tonsillitis, pharyngitis) and skin infections associated with susceptible staphylococcal or streptococcal strains.

CONTRAINDICATIONS

Vibramycin is contraindicated in individuals who have shown hypersensitivity to tetracyclines.

WARNINGS

As with other tetracyclines, Vibramycin may produce brownish discoloration of teeth in any bore-forming tissue, though in vitro it binds calcium less strongly than other tetracyclines. Though not observed in clinical studies to date, it should be anticipated that like other tetracyclines the use of Vibramycin during tooth development (last trimester of pregnancy, during lactation, necrotizing ulcerative gingivitis) may cause discoloration of the teeth. More commonly associated with long-term use of tetracyclines, this side effect has also been known to occur after short courses.

PRECAUTIONS

In clinical studies to date, Vibramycin administration did not lead to increased serum levels nor to an increase in the serum half-life of doxycycline in patients with impaired renal function. Vibramycin in normal dosage may be used to treat these patients. Although no evidence of increased toxicity has been observed in such patients, the potential for increased hepatic or renal toxicity should be considered until further data on the metabolic fate of doxycycline under these conditions becomes available. Liver function tests should be carried out at regular intervals in patients receiving high doses for prolonged periods of time. Concurrent administration of Vibramycin and agents known to be hepatically toxic should be avoided if possible. The use of antibiotics may occasionally result in overgrowth of non-sensitive organisms; thus, observation of the patient is essential. There is evidence to suggest that Vibramycin, may have less effect on the gut flora than other tetracyclines. Vibramycin should not be administered to pregnant and lactating women or neonates until its safety in such cases has been established beyond all reasonable doubt, unless in the judgment of the physician the potential benefit to the patient outweighs the risk to the fetus or child. Certain photosensitive individuals may develop a photosensitive reaction to sunlight during treatment with Vibramycin. If this or any other allergic reaction should occur, medication should be discontinued. Increased intravascular pressure with bulging fontanelles has been observed in infants receiving therapeutic doses of tetracycline. Although the mechanism of this phenomenon is unknown, the signs and symptoms have dissipated rapidly upon cessation of treatment with no sequelae.

ADVERSE REACTIONS

As with other broad-spectrum antibiotics, gastrointestinal disturbances such as nausea, vomiting and diarrhea, as well as glomerulonephritis, stomatitis and pneumonia, may occur but have rarely been sufficiently troublesome to warrant discontinuation of therapy. As with other tetracyclines, elevation of SGOT or SGPT values, anemia, neutropenia, eosinophils, leukopenia or elevated BUN has been reported, the significance of which is not known.

SYMPTOMS AND TREATMENT OF OVERDOSE

Gastric lavage if necessary.

DOSAGE AND ADMINISTRATION

The recommended dosage of oral Vibramycin in adults for the majority of susceptible infections is a single loading dose of 200 mg on the first day of therapy followed by a maintenance dosage of 100 mg daily at the same time each day thereafter. The recommended dosage schedule for children over one month weighing up to 50 kg is a single loading dose of 3 mg/kg of body weight on the first day, followed by a maintenance dosage of 2.5 mg/kg once daily at the same time each day thereafter. As absorption is not significantly affected by food or milk, Vibramycin should be given with or after a meal thus minimizing the possibility of gastric upset. Anthraquin and iron preparations impair absorption and should not be given concomitantly to patients taking oral Vibramycin. In severe infections in adults, such as lung abscesses or osteomyelitis, and in chronic urinary tract infections, a single daily dose of 200 mg may be used throughout. For more severe infections in children, up to 5 mg/kg of body weight may be given. Therapy should be continued after symptoms and fever have subsided. It should be noted, however, that effective antibacterial levels are usually present 24 to 36 hours following discontinuance of Vibramycin therapy. When used in streptococcal infections, therapy should be continued for 10 days to prevent the development of rheumatic fever or glomerulonephritis. No alteration in recommended dosage schedule need be made when treating patients with impaired renal function.

DOSE FORMS

Vibramycin capsules are available as 100 mg (blue) hard gelatin capsules containing doxycycline hyclate equivalent to 100 mg of doxycycline, supplied in bottles of 50 and 200. Vibramycin for oral suspension (doxycycline monohydrate) is available as a powder for oral suspension containing, when reconstituted, doxycycline monohydrate equivalent to 25 mg of doxycycline/5 mL (each teaspoonful) with a pleasant raspberry flavor in 50 mL bottles.

Reference


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