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Hypothalamic dysfunction in a child: a distinct syndrome?

Report of a case and review of the literature

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Abstract. We report the case of a 9-year-old girl with multiple problems due to hypothalamic dysfunction of obscure origin: apnoeic spells, behavioural problems, developmental delay, hypodipsia with bouts of hypernatraemia, episodes of spontaneous hypothermia, obesity, petit-mal seizures, non-progressive precocious puberty, absence of respiratory response to CO_2 and probably insensitivity of hyposensitivity to pain. She also had hyperprolactinaemia and decreased human growth hormone secretion. Hypothyroidism of central origin and hyposecretion of cortisol were also present. Multiple brain CT-scans failed to reveal any tumour or other anatomical abnormality. Her clinical course was improved initially by treatment with clomipramine, but she died suddenly, and the autopsy failed to disclose any anatomical lesion. We compare this case with three similar previously reported cases.

Key words: Hypothalamic dysfunction – Hypothalamus

Introduction

We report a case of hypothalamic dysfunction of obscure origin in a 9-year-old girl and compare her features with those of three previously reported boys with similar problems [1–3].

Case report

A 9-year 4-month-old girl was transferred to Ste-Justine hospital because of hypothalamic dysfunction of unknown origin.

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Abbreviations: ACTH = adrenocorticotropin; ADH = antidiuretic hormone; E_2 oestradiol; FSH = follicle stimulating hormone; HGH = human growth hormone; LH = luteinizing hormone; T_4 = thyroxine; TSH = thyroid stimulating hormone

The family history was non contributory. She was born at term after a normal pregnancy, and during delivery she aspirated meconium. When she was 4 years of age, she was seen by a psychologist because of multiple problems including hypersomnia, immaturity, developmental delay and behavioural difficulties consisting of alternating aggressivity and passivity. She was obese and had symptoms compatible with petit-mal seizures, which was confirmed by EEG. Treatment with valproic acid was initially successful. She had multiple episodes of urinary tract infection without underlying anatomical abnormality. At age 6, she underwent surgery for correction of strabismus. When asked about sensitivity to pain, her mother stated that her daughter never cried as a result of falls.

At the age of 6 years and 8 months, she was seen by a paediatric endocrinologist because of precocious puberty; she also had a transient episode of hypernatraemia. At that time, she was obese: her height was 119 cm (75th percentile), and her weight was 34.5 kg (above the 97th percentile, 156% of ideal weight). Her head circumference was 51.5 cm (50th percentile). Her bone age was 5 years and 9 months. She had premature sexual development (Tanner stage II for breasts and pubic hair); the physical examination was otherwise normal. The following investigations yielded normal results: intravenous glucose tolerance test, serum cortisol, adrenocorticotropin (ACTH), triiodothyronine, thyroid stimulating hormone (TSH), luteinizing hormone (LH), follicle stimulating hormone (FSH), and dehydroepiandrosterone; serum thyroxine; (T_4) was not available for technical reasons; plasma prolactin was elevated (72 and 78 µg/l, or 8 mIU/ml), as well as serum oestradiol (E_2) (95 pmol/l). The cerebral CT-scan was normal, and the EEG was typical of petit-mal seizures.

Behavioural problems continued and, at the age of 7 years and 2 months, enuresis was still present despite therapeutic trials with imipramine and with an alarm system. Her performance in school was poor and the seizures were not well controlled until valproic acid was replaced with ethosuximide. Her height was now 123 cm (75th percentile) and her weight had reached 41 kg (above the 97th percentile, 170% of ideal weight). Pubertal development had not progressed, and bone age had increased to 7 years. Serum sodium concentration was 144 mmol/l. Plasma prolactin was still elevated (43 µg/l). After administration of L-dopa (500 mg/m^2), plasma human growth hormone (HGH) level remained at baseline (2 µg/l) at 60, 90 and 120 min, while plasma prolactin decreased from a basal concentration of 48–10 µg/l after 120 min. During stimulation with luteinizing hormone-releasing hormone (100 µg), serum LH concentration increased from a baseline value of 6 to 14 IU/l at 90 min, and plasma FSH levels increased from a baseline level of 6–20 IU/l at 90 min; this response is compatible with true precocious puberty of hypothalamic origin.

At the age of 8 years and 6 months, her behaviour remained unchanged and her seizure disorder was under control, but enuresis was still a problem. Her height was 130 cm (75th percentile), and her weight was 43 kg (above the 97th percentile, 153% of ideal weight). Her pubertal development was still at Tanner stage II. Her bone age was 8 years and 10 months. Serum LH, FSH and E_2 were normal. Plasma prolactin remained elevated (47 µg/l). Serum triiodothyronine was normal, serum T_4 was low (58 nmol/l), but serum TSH level was within normal limits, and antithyroid antibodies were absent. A thyrotropin releasing hormone stimulation test (100 µg) showed a late response with an increase in serum TSH level from 5 to 59 mU/l at 45 min; plasma prolactin also increased from 45 to 72 µg/l after 30 min. Because of the low T_4 level and the late response of TSH to thyrotropin releasing hormone stimulation, central hypothyroidism was considered likely, and treatment with L-thyroxine was started.

At the age of 9 years and 2 months, during a follow up visit, her mother reported that she was less aggressive. Her sleep-wake cycle was inverted, and enuresis was still present. There was no polydipsia or polyuria. Pubertal development was still at Tanner stage II. He obesity had improved: her height was 133 cm (75th percentile) and her weight was 44 kg (above the 97th percentile, 141% of ideal weight). The physical examination was otherwise normal, except for a single café-au-lait spot (coast of California type), measuring 3 by 3 cm, on her right buttock. Serum sodium was 155 mmol/l, potassium 4.1 mmol/l, chloride 113 mmol/l, an plasma glucose 4.2 mmol/l. Urine specific gravity was 1015. Plasma prolactin level remained elevated (44 µg/l). Serum LH and plasma FSH remained in the normal range. Serum E_2 was elevated (107 pmol/l). Under treatment, thyroid function tests were normal. A few days after this visit, this child was admitted because of severe hypothermia (30.5°C) associated with confusion. Serum sodium was 149 mmol/l, potassium 5.3 mmol/l, and chloride 114 mmol/l. Plasma osmolality was 303 mmol/kg, and urine osmolality was 896 mmol/kg. Body temperature normalized with the use of a heating blanket. Two weeks later, she had a generalized tonic-clonic seizure with apnoea and bradycardia, for which she was intubated. The neurological examination did not disclose any abnormality. Serum sodium was 129 mmol/l, potassium 4.4 mmol/l, chloride 100 mmol/l, and total CO_2 21 mmol/l. Treatment with carbamazepine was started. She was extubated 24 h after this incident, but required continuous oxygen administration. Two days after extubation, she had another episode of altered state of consciousness with apnoea, bradycardia and respiratory acidosis (pH: 7.16 and PCO_2: 96 mm Hg). She had to be reintubated and mechanically ventilated. EEG and CSF examination were normal. During the next few days, she had few spontaneous respirations and weaning from the respirator was impossible. Doxapram was given. Extubation was achieved only after treatment with oral methylphenidate was instituted. MRI of the brain was normal. The child was then transferred to Ste-Justine hospital.

At the time of her admission at the age of 9 years and 4 months, the child was obese, withdrawn, and very hypoactive. Her pubertal development was still at Tanner stage II, her height was 134 cm (75th percentile), and her weight was 47.8 kg (above the 97th percentile; 170% of her ideal weight); her temperature and vital signs remained normal throughout her hospitalization, and her usual medical treatment was continued (methylphenidate: 5 mg every 6 h, carbamazepine: 200 mg every 12 h, L-thyroxine: 0.1 µg every 24 h, a forced fluid intake of 1500 ml/day and a heating blanket during sleep). Plasma sodium remained within normal limits; the highest urine specific gravity was 1027. Hypercapnia was noted several times, especially during sleep (the highest PCO_2 was 56 mm Hg). Visual fields, skull X-rays and brain CT-scan with infusion were all normal. The CSF was unremarkable; at the time of the lumbar puncture, the child did not seem to feel pain. There was no ventilatory response to CO_2. The EEG showed generalized bursts of wave-spikes typical of petit-mal.

A literature search revealed three similar cases [1–3], one of them apparently responding to clomipramine. On discharge, the referring physician was advised to start this medication and to wean the child from methylphenidate under close surveillance in the hospital.

During the next few months, the child was put on clomipramine, starting with 10 mg every 12 h, and she was successfully weaned from methylphenidate. During this period, she did not have any episode of severe hypothermia or apnoea and some improvement in behaviour was noted.

At the age 9 years and 7 months, the patient was readmitted to the referring hospital. On admission, she was hypernatraemic (plasma sodium varied between 158 and 165 mmol/l) with a urine specific gravity of 1020. She was encouraged to drink 2000 ml of fluids per day, after which her natraemia returned to normal limits and her urine specific gravity fell to 1000. During this hospitalization, further testing of her endocrine functions was carried out: absence of nocturnal pulsatility of plasma HGH, LH, FSH an prolactin was noted; the HGH level remained stable at 2 µg/l; serum LH and FSH were normal, but plasma prolactin levels had decreased (24 and 28 µg/l) since treatment with clomipramine was started. Plasma E_2 remained elevated (108 pmol/l). At 8:0 a.m., 16:00 p.m. and 24:00 p.m., plasma ACTH levels were low (16, 10, and 11 pmol/l, respectively), and serum cortisol, measured at the same time, was also low (37, 14, and 16 nmol/l, respectively). Plasma dehydroepiandrosterone and serum aldosterone were both normal. Thyroid function had remained normal under L-thyroxine treatment. During an arginine stimulation test (0.5 g/kg), plasma HGH did not rise above the basal level (2 µg/l) throughout the entire 90 min period. During an insulin stimulation test (0.05 units/kg), plasma HGH also remained at the basal level (2 µg/l) during the 60 min period, while serum cortisol rose from 46 to 106 nmol/l after 60 min; plasma glucose fell from 4.1 to 1.7 mmol/l. Due to these low cortisol levels, treatment with cortisone was started.

At the age of 10 years and 2 months, she was treated with L-thyroxine (0.15 µg every 24 h), cortisone (20 mg per day in three divided doses), carbamazepine (200 mg every 12 h), and clomipramine (30 mg every 12 h). A low calorie diet was followed, with ingestion of 1500 ml of fluids per day. She was doing relatively well, but her mother reported that she became irritable or drowsy and that her body temperature dropped to 32°–34°C each time she tried to reduce the dose of clomipramine from 30 to 20 mg every 12 h. On examination, her temperature was 32.7°C, her height was 136 cm (50th percentile) and her weight was 47.5 kg (97th percentile, 139% of ideal weight). Pubertal development was stable at Tanner stage II. Serum sodium was 128 mmol/l, potassium 4.3 mmol/l, and chloride 88 mmol/l. Plasma glucose was 3.8 mmol/l. Serum osmolality and 264 mmol/kg, and urine osmolality 128 mmol/kg. Clomipramine was increased to 40 mg every 12 h and a reduction in water intake was recommended.

At the age of 10 years and 7 months, the child died suddenly at home. The autopsy failed to disclose any lesion. Histological examination of the brain, including the hypothalamic area, was normal.

Discussion

This child had obvious clinical evidence of hypothalamic dysfunction. She lacked appetite control and became obese; she also experienced hypodipsia with resulting hypernatraemia in the absence of diabetes insipidus. Maintenance of body temperature was difficult leading to severe episodes of hypothermia. Insensitivity to CO_2 led to repeated episodes of apnoea, probably aggravated by oxygen therapy. By history she also probably had hyposensitivity or insensitivity to pain. Evidence of a progressive hypothalamic dysfunction was first noted when signs of premature puberty developed, associated with hypeprolactinaemia. Later, decreased production

Table 1. Clinical and laboratory features of the four published cases

	Gurewitz et al. [2]	Dunger et al. [1]	Schaad et al. [3]	Present study
Ethnic origin	Jewish Yemenite	British	Swiss	French Canadian
Sex	Male	Male	Male	Female
Age of presentation	4 years	4 years	6 years	4 years
Behavioural abnormalities	+	+	+	+
Episodes of hypothermia	+	+	− (Hyperthermia)	+
Central apnoeas	+	−	−	+
Hypodipsia, hypernatraemia	+	+	+	+
Hyposensitivity to pain	+	+	+	+
Obesity	+	+	+	+
Chronic hypercapnia	+	+	−	+
Respiratory response to CO_2	None	None	Not measured	None
Central hypothyroidism	+	+	−	+
Hyperprolactinaemia	+	+	Not measured	+
HGH deficiency	+	+	+	+
Cortisol secretion	Normal	Decreased	Normal	Decreased
Brain CT-scan	Normal	Normal	ND	Normal
MRI	ND	ND	ND	Normal
Carotid angiography	ND	ND	Normal	ND
Pneumoencephalography	ND	ND	Normal	ND
EEG	Abnormal	Abnormal	ND	Abnormal
Autopsy	ND	ND	ND	No anatomical lesion

ND, Not done

of HGH and possibly of ACTH, TSH, LH and FSH were noted and pubertal development failed to progress. Multiple brain CT-scans as well as one MRI of the brain, performed over a 4-year period, failed to identify any anatomical abnormality. The absence of lesion was confirmed at autopsy.

To our knowledge, only three similar cases have been described in the literature [1–3]; their main features, as well as those of our case are summarized in Table 1. We report the first girl affected by this syndrome. All four children presented with obesity around the age of 4–6 years, and had behavioural problems, including hypersomnia. Except for the case described by Schaad et al. [3] who had persistent hyperthermia, all others had life-threatening episodes of hypothermia. All four patients seemed hyposensitive or insensitive to pain. A striking characteristic of three patients was chronic hypercapnia, with absent ventilatory response to CO_2. It is important to note that oxygen administration to these patients may have catastrophic consequences. All four had thirst regulation problems with episodes of serum sodium imbalance; they may also have episodes of inappropriate secretion of antidiuretic hormone (ADH). The endocrine dysfunctions of three of these children were similar, including central hypothyroidism and hyperprolactinaemia. All four had HGH deficiency. Our patient appears to be the only child needing cortisone replacement. It was not possible in any of these patients to document any tumoural or other anatomical abnormality, even after prolonged follow up an multiple CT-scans of the brain or other neuroradiological investigations. Only in our patient was autopsy performed, confirming the absence of a lesion.

Dunger and his colleagues [1] suggested that this syndrome may be due to increased local activity of opiate peptides in the central nervous system. They pointed out that many features such as hyposensitivity to pain, inadequate respiratory control and behavioural problems resemble opiate toxicity. They found normal levels of metenkephalin and C-terminal lipotrophin in blood and CSF, but underline the fact that these concentrations may not reflect their concentrations in the brain. Furthermore, endogenous opiate peptides generally inhibit the secretion of hypothalamic and pituitary hormones.

On the basis of the hypothesis of opiate system disturbances, it was logical to consider whether these patients could be helped by drugs, in addition to multiple hormonal replacement. In one patient, naloxone, an opiate antagonist, seemed to reverse the respiratory depression as well as water and electrolytes disturbances; in the same patient, it seemed to lower the pain threshold [1]. Naloxone should probably be used during acute episodes of respiratory depression or hypothermia. The effect of continuous treatment with other opiate antagonists such as naltrexone remains to be studied. In one case [1], bromocriptine, a dopaminergic agonist, reduced prolactinaemia but seemed to induce severe hypothermia and precipiate inappropriate ADH secretion. In the same patient, amphetamine increased the level of activity of the child, but resulted in seizures and inappropriate ADH secretion. In one case, clomipramine therapy seemed to permanently normalize the ventilatory re-

sponse to CO_2 and to prevent apnoeic episodes, but did not improve the others problems [2]. Our patient also seemed to benefit, at least transiently, from clomipramine, but this apparent improvement may also be attributed to the natural course of the disease. Gurewitz and his colleagues [2] selected this form of therapy because of reports suggesting an improvement of sleep apnoea by tricyclic antidepressants. These authors believe that this arousal effect occurs through the opiate receptor system.

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