Unusual association of diseases/symptoms

Haematological, neurological and electrocardiographic findings in secondary hypothermia

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Summary

The association between secondary hypothermia and pancytopenia is uncommon. A young woman presented with chronic hypothermia (28.8–34.6°C) secondary to surgical hypothalamic injury postcraniopharyngioma resection as a child. Associated findings included pancytopenia (haemoglobin 8.1 g/dl, leucocytes 3500/mm³, platelets 63 000/mm³), ataxia, upper motor neuron signs, decreased level of consciousness and new ECG changes. An extensive evaluation failed to reveal any cause of pancytopenia other than chronic hypothermia. The haematological and neurological changes improved after active rewarming.

BACKGROUND

The association of pancytopenia, neurological disturbance and ECG changes with hypothermia is rare. These clinical manifestations have been documented primarily in patients with intraoperative hypothermia or in victims of exposure hypothermia. However, in patients with secondary hypothermia, analogous physiological disturbances may also occur. Early diagnosis is essential in order to initiate active rewarming and supportive management.

CASE PRESENTATION

A young woman with developmental delay and postsurgical pan-hypopituitarism secondary to craniopharyngioma tumour resection as a child presented with 6 months history of progressive cognitive decline, apathy and altered mental state. During this time, her parents observed her exhibiting pronounced right-sided weakness, personality changes, lethargy and impaired balance leading to frequent falls. They also described episodes of menometrorrhagia, with the most recent episode lasting 8 days. Nine months prior to admission, the patient was moved to a group home. Soon after, the patient started developing personality changes. These symptoms were initially attributed to the acute stress induced by change in the living environment. Also, the pre-existing neurological deficiencies, post craniotomy and large tumour resection, made detection of hypothermia-induced neurological alterations more challenging to diagnose. On the day prior to admission, the patient suffered a fall at her group home. She was found to be unresponsive and profoundly hypothermic (28.8–31.1°C per rectum). She was resuscitated with stress-dose steroids, warming blankets and antibiotics. On admission, the patient was fully oriented with an oral temperature of 34.6°C but exhibited a marked inattentiveness, a frequent fixed gaze at inanimate objects and poor participation in the history-taking process. Cerebellar tests (finger-nose-finger, heel-to-shin manoeuvres) were worse on the right than left; right shoulder shrug was weak. There was an asymmetric

smile with right facial drop. Proximal and distal muscular strength was 3/5 on the right upper and lower extremities and 5/5 on the left. Generalised hyporeflexia, right Babinski sign and right pronator drift were documented. The remainder of the physical examination was unremarkable.

INVESTIGATIONS

On biochemical investigation, hypernatraemia, hyperchloraemia and hypoalbuminaemia (albumin 3.3 g/dl) were deemed, most likely, secondary to dehydration and decreased oral intake, consistent with the patient's history of weakness and lethargy (table 1). The complete blood count was pertinent for anaemia (haemoglobin 8.1 g/dl), leukopenia (leucocytes 3500/mm³) and thrombocytopenia (platelets 63 000/mm³) (table 1). The reticulocyte count was 3.6% however the reticulocyte index was 1.5. A peripheral smear confirmed a normocytic normochromic anaemia, moderate to marked thrombocytopenia and scattered toxic-granulated neutrophils. Other lab tests identifying other causes of pancytopenia, such as antibody testing for Epstein-Barr virus, cytomegalovirus, parvovirus and HIV were all negative. Vitamin B12, folate levels and iron studies were normal. Thyroid stimulating hormone was undetectable owing to postsurgical panhypopituitarism, but T3 total and free T4 were within normal limits. The ECG recording (figure 1) revealed new abnormalities when compared with an ECG recorded 1 month back. Sinus bradycardia, PR interval prolongation, moderate QRS widening and a prolonged QT interval were noted. A head MRI revealed prior frontal craniotomy and extensive hypothalamic injury secondary to craniopharyngioma resection. There was no evidence of tumour recurrence but the hypothalamic region was entirely absent. These findings confirmed our patient's suspected hypothalamic dysfunction manifested by the inability to regulate her own temperature, lack of cold sensation, lack of shivering as well as the indiscriminant, exaggerated appetite that was observed during the hospital course.

Table 1 Lab results at hospital admission, 24 hs after active rewarming and after 7 days of active rewarming

	Temp °C	Hg (g/dl)	RBC ($\times 10^6$ /l)	RDW %	WBC (/mm ³)	PLT $\times 10^3$ (/mm ³)	RI (%)	HTC (%)	Na (mmol/l)	K	Cl
Admission	34.6	8.1	3.05	18.1	3500	63	1.5	25.6	147	3.6	111
24 h after rewarming	35.6	10	3.7	17.1	4900	67	—	31.5	139	4.1	106
7 days after rewarming	35.6	10.5	3.82	16.9	5400	152	—	32.1	126	4.1	94

HTC, haematocrit, PLT, platelets; RBC, red blood cell; RDW, red cell distribution width; WBC, white blood cell.

DIFFERENTIAL DIAGNOSIS

In this case, the initial personality changes could be attributed to the acute stress induced by change in the living environment. Adding to this clinical conundrum, her acute functional decline and decompensation could be attributed to an Addisonian crisis superimposed on chronic adrenal insufficiency; but this classically manifests with hypotension, tachycardia, nausea, vomiting, diarrhoea and hyponatremia, findings not present in our patient. In this case, the delayed presentation of secondary hypothermia and its complications suggests that failure of compliance with medications or new environmental living conditions may have played a triggering role.

TREATMENT

After adequate intravenous fluid resuscitation, nutrition and active body rewarming with electric blankets, the patient's core-body temperature increased and remained stable at 35.6°C. The hormonal replacement treatment for her panhypopituitarism was continued throughout hospital stay and included: hydrocortisone, levothyroxine, desmopressin, somatostatin and estradiol-levonogestrel.

OUTCOME AND FOLLOW-UP

Gradually, following the active rewarming treatment, the patient became less lethargic, more communicative and her right-sided strength improved. The upper motor neuron findings resolved. After 7 days of active rewarming,

Figure 1 Upper tracing—baseline ECG 1 month prior to hospital admission: sinus rhythm, rate=62 bpm; PR=190 ms, QRS=110 ms; Lower tracing—ECG changes at hospital admission: sinus bradycardia, rate=50 bpm, prolonged PR interval=220 ms, widening of QRS complex=130 ms with irregularity in terminal S wave of anterior precordial lead V1 and moderately prolonged QTc interval (approximately 450–470 ms).

the white cell and platelet count returned to normal values and pancytopenia resolved (table 1). Only moderately low haemoglobin and red blood cell levels were present, but they were following an ascending trend. These were probably due to the patient's ongoing vaginal bleeding. A bone marrow biopsy was not pursued due to resolution of pancytopenia.

DISCUSSION

This report describes findings from a young adult patient in whom central hypothermia secondary to surgical craniopharyngioma resection was associated with pancytopenia (table 1), ataxia, upper motor neuron signs, decreased level of consciousness and new ECG changes. An extensive evaluation failed to reveal any causes of pancytopenia or neurological changes other than chronic hypothermia. To date, the specific association between hypothermia and pancytopenia has been reported in the literature in only eleven cases; in five of these cases, pancytopenia occurred in association with secondary hypothermia. We describe a sixth case in which haematological changes were accompanied by new neurological and ECG findings. The haematological and neurological changes in the previously published cases were similar to the findings in our patient, but none reported concomitant ECG abnormalities. In these cases, thrombocytopenia and leukopenia were consistent findings but the degree of anaemia was variable.

Normal body temperature is a reflection of a delicate balance between heat production and heat loss, many of the chemical and biological reactions necessary for human survival only occurring within these physiological temperature ranges. Hypothermia (body temperature less than 35°C) is classified as 'primary' when due to environmental exposure (accidental hypothermia), or as 'secondary', if due to a medical illness (sepsis, stroke, brain tumours and hypopituitarism). A third form of hypothermia, increasingly more common is termed 'therapeutic' and is used to reduce ischaemic-hypoxic injury during cardiac surgery, neurosurgery or resuscitated cardiac arrest. The posterior hypothalamus initiates thermogenesis through shivering and increased basal metabolic rate. If

part of the hypothalamic synapse network is disrupted, thermoregulation can still occur (through brainstem and cervical cord pathways), but with less integration and, therefore, less precision.¹ In previously published cases, direct hypothalamic injury leading to secondary hypothermia was caused by stroke,²⁻³ multiple sclerosis,⁴⁻⁵ brain tumours⁶⁻⁷ and traumatic brain injury⁸⁻⁹ (table 2).

Initial interest in hypothermia-induced pancytopenia arose in the 1950s when hypothermia was first introduced as an adjunct to anaesthesia during cardiac surgery. On the basis of previous animal research studies, volume depletion stimulated by cold-induced antidiuretic hormone suppression can lead to hypovolaemia, the haematocrit increasing by about 2% for every 1°C decline in temperature.¹⁰ Abnormal haematocrit in a moderate or severely hypothermic patient could suggest a pre-existing anaemia or blood loss. In this case, at hospital admission the haematocrit was low and improved with rewarming, reflecting a significant amount of blood loss due to the patient's history of severe menorrhagia. This could also be supported by increased red cell distribution width (18.1%) in the presence of a normal mean corpuscular volume (83fl) (table 1). Also, hypothermia may impair both the endothelial synthesis of prostacyclin PGI₂ and platelet production of thromboxane B₂,¹¹ promoting platelet activation and thrombosis and a decline in platelet activity with falling temperatures. Research studies concluded that thrombocytopenia can occur from platelet sequestration in the liver and spleen but could also be related to marrow suppression. Leucocyte depletion in response to hypothermia has been documented and studies suggest that neutrophil migration, white cell margination and bacterial phagocytosis¹² are impaired in cold temperatures, predisposing to infection. Bone marrow suppression and progressive bone marrow failure have also been reported in patients with hypothermia.¹³ This could be the cause for erythroid hypoplasia and normocytic normochromic anaemia. It is still unclear why a low body temperature should cause bone marrow failure, and further studies are needed to assess the effects of prolonged hypothermia on marrow activity, cytokine levels

Table 2 Summary of haematological findings associated with hypothermia in previously published case reports

Year	Journal	Author	Age/sex	Cause of hypothermia	Core temperature (°C)	Haemoglobin concentration (g/dl)	WBC (/mm ³)	PLT ×10 ³ (/mm ³)	Bone marrow
1982	<i>British Journal of Haematology</i>	O'Brien <i>et al</i> ¹³	46 F	Unknown	35	8.9	3500	low	Erythroid hypoplasia
			61 F	Multiple sclerosis	29.4	12.9	6800	19	Same
			24 M	Unknown	31.8	13.5	3500	32	Same
1985	<i>Southern Medical Journal</i>	Rosenkrantz ¹⁶	63 F	Accidental	32.2	6.7	1300	40	Hypocellular fatty marrow
			64 M	Accidental	33.4	10	1500	100	Hypoplastic
1985	<i>British Medical Journal</i>	Easterbrook <i>et al</i> ¹⁷	82 F	Accidental	27	13.2	5800	33	—
			83 F	Accidental	31.9	15.9	4800	62	—
1988	<i>Clinical Pediatrics</i>	Holm ¹⁸	5.4 M	Herpes encephalitis	34	6.7	2000	97	Hyperplastic
			7.4 F	<i>Escherichia coli</i> meningitis	32	—	3800	7	Hypoplastic
1988	<i>Postgraduate Medical Journal</i>	Griffiths <i>et al</i> ⁸	40 M	Post-tumour resection	31.4	10.5	2100	51	Hypoplastic
2002	<i>Journal of Pediatric Haematology/Oncology</i>	Lo <i>et al</i> ⁹	8 F	Post-tumour resection	31.4	7.8	2500	207	Mild, erythroid hypoplasia

and blood cell survival. In this case, at admission, the reticulocyte index was inappropriately low (1.5) for the patient's degree of anaemia reflecting bone marrow suppression.

Cognitive dysfunction is common during hypothermic episodes. In three of the previously reported cases,^{8 9 13} the neurological abnormalities were similar to our patient: limb and plantar spasticity, right-arm and right-leg myoclonus and absence of lower limb reflexes and ataxia. The central neurological effects of hypothermia can also include confusion and amnesia. In part, this may be related to a reduction in cerebral blood flow by 6–7% per 1°C decrease in temperature. Ataxia and loss of fine motor control are also seen in the initial stages, followed by hyporeflexia, an extensor plantar response and pupillary sluggishness in moderate stages of hypothermia,¹⁴ and as the temperature falls, rigidity, pupillary dilation and areflexia may appear. These changes are explained by cold-induced, impaired peripheral nerve conduction and velocity.¹⁵ In all previously described cases, haematological and neurological recovery coincided with the temperature returning to normal.

ECG findings have not previously been reported in association with secondary hypothermia, but are not unexpected. In this case, the ECG revealed some of the classic manifestations related to hypothermia: sinus bradycardia (heart rate 51 bpm), prolonged PR interval (240 ms), QT/QTc intervals (520/480 ms) as well as modest widening of the QRS complex (116 ms) (Image). Although a J-wave (Osborn wave) was not present, the upward-curving slope of the S wave in lead V1 could mimic the initial characteristic changes induced by hypothermia. These ECG changes related to hypothermia are thought to be induced by the prolongation of action potential duration, delayed activation of the repolarising potassium current and intracellular potassium shift, all contributing to a prolongation of the PR and QT intervals.

Learning points

- ▶ Secondary hypothermia-induced pancytopenia is uncommon and its diagnosis requires a high degree of clinical suspicion.
- ▶ ECG changes may also be expected in secondary forms of hypothermia.
- ▶ Haematological, neurological and ECG abnormalities due to hypothermia should resolve with appropriate therapeutic rewarming.

Competing interests None.

Patient consent Obtained.

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