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Pheochromocytoma and hypoglycemic fits. A case report

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Introduction. Pheochromocytomas often induce hyperglycemia. Few cases are reported with hypoglycemic fits. The mechanism is unknown. Our findings may indicate mechanisms.

The patient. A 37 year old female was referred to us because of unstable blood glucose values. It turned out that she had a pheochromocytoma with typical characteristics: Attacks (Table 1), hypertension (Fig 1), electrocadiogram indicating ischemia, normal coronary arteries in dynamic CT, normal Echo-Doppler heart examination, diabetes with HbA1c 6.6 % and fasting blood glucose 8.8 mmol/l, high catecholamines, with adrenaline dominating (Tables 2 and 4), MR: pheochromocytoma (45 mm) in right adrenal, MIBG-scintigraphy: no extraadrenal signal.
In addition to this typical presentation she developed frequent hypoglycemic fits (Table 1, Fig 3) induced by sweet meals and increased endogenous insulin release (Table 3). A mixed meal triggered a large insulin and catecholamine response. (Table 4). Her tumor contains clusters of cells staining positive for antibodies to insulin (Fig 2). Preoperative α-adrenergic blockade with doxazocin normalized blood pressure and abolished her typical pheochromocytoma attacks, while her hypoglycemic fits persisted. Because of moderate tachycardia and electrocardiographic abnormalities β-adrenergic blocking was intended and considered safe when α-blockade was effective. However, after the first tablet of propranolol 20 mg she developed a severe attack with hypertension, pallor, sweating, headache, vomiting and takotsubo cardiomyopathy. Intravenous nitroglycerine curbed the attack.
After removal of her pheochromocytoma she has been healthy, with normal blood glucose values and without hypoglycemic fits.

Table 1

Characteristics of her two types of fits

	Typical pheochromocytoma fits	Hypoglycemic fits
Symptoms frequent > less frequent	Hot and sweating > restlessness > headache > nausea > vomiting > palpitations	Vertigo > attention deficit > diplopia > palpitations
Relationship to meals	Less than half an hour after meals	Less than two hours after sweet meals
Time of day	Mainly in the morning never at night	Mainly late afternoon never at night
Blood glucose	Not hypoglycemic	1.8 – 3.9 mmol/l
Relieved by	Fading spontaneously	Taking carbohydrates
Frequency	Up to several times a week	Up to several times a week
History	For two years, with progression	For one year, with progression
Effect of α-adrenergic blocking	Eliminated	Persisted
Effect of adding a β-adrenergic blocker (20 mg propranolol)	A severe attack complicated with takotsubo cardiomyopathy and hyperglycemia	
Cured by	Tumor removal	Tumor removal

Table 2

Estimates of catecholamine production

	The patient	Upper reference value	Ratio
Plasma metanephrine nmol/l	6.51	0.71	9
Plasma normetanephrine nmol/l	5.25	1.09	5
Urine adrenaline nmol/24 hours	2635	127	21
Urine noradrenaline nmol/24 hours	2238	723	3

Table 3

Sweet meal challenge (late afternoon)

90 minutes after 75 g of chocolate she felt hypoglycemic

Blood glucose	1.8 mmol/l
Plasma insulin	47 pmol/l
C-peptide	1012 pmol/l

Table 4

Mixed meal challenge (morning)

		Minutes				
	Upper ref value	0	20	90	120	Ratio max/ref
Blood glucose mmol/l	7.0	8.7		16	12	
Plasma insulin pmol/l	160	21		269	695	
Plasma C-peptide pmol/l	1480	339		1543	3205	
Plasma adrenaline pmol/l	490	1057	2730	2511	800	5.6
Plasma noradrenaline pmol/l	2867	1587	5248	3223	1213	1.8

Fig 1

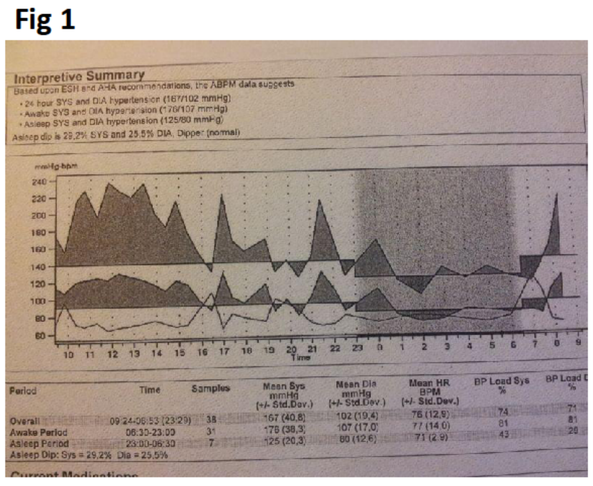

Fig 1. 24 hour blood pressure. High values mainly in the morning

Fig 2

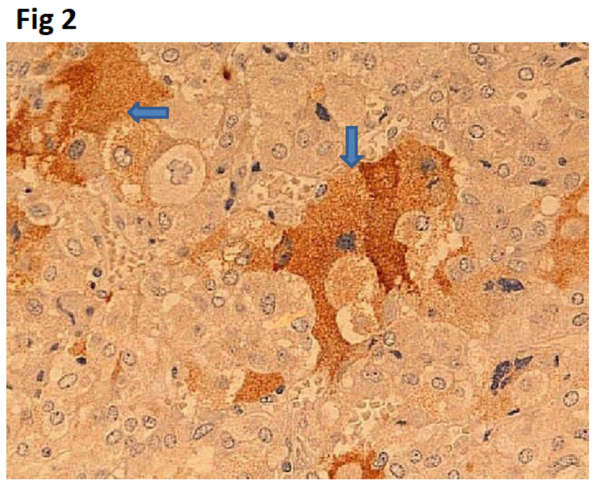

Fig 2. Clusters of cells (blue arrows) in the tumor. Immunostaining positive for anti-insulin

Fig 3

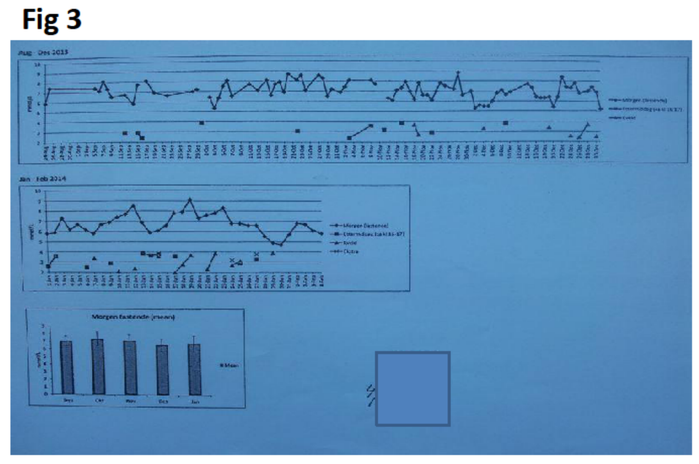

Fig 3. The patient s own fasting blood glucose registrations over the last 6 months (upper curve) and of frequent hypoglycemic events in the afternoon (lower part of panel, single measurements). Average of fasting values were about 7 mmol/l (lower graph) and hypoglycemic values were 2.0-3.9.

Conclusions

1. Our pheochromocytoma patient had the rare variant with hypoglycemic fits.
2. Endogenous hyperinsulinemia caused her hypoglycemic fits.
3. Her tumor has cells which appear to contain insulin; this may have caused her hyperinsulinemia.

Possible mechanisms contributing to her hypoglycemic fits

1. Symptoms and blood pressure indicate that high levels of catecholamine prevailed during morning hours. This may have emptied her liver glycogen stores, rendering her more susceptible to hypoglycemia which only occurred during the late afternoon and evening.
2. Pheochromocytoma patients can develop hypoglycemia postoperatively, probably caused by abrupt fall in the catecholamine suppression of insulin release mediated by α2-adrenergic receptors on insulin producing cells. Our patient seems to have had a similar reduction of catecholamine output in the afternoon.
3. Adrenaline dominated over noradrenaline. Adrenaline stimulates β2-adrenergic receptors known to stimulate insulin release. This may have contributed to her hyperinsulinemia.
4. Persistence of hypoglycemic fits on alphablockade strenghtens the possibilities of mechanisms 2 and 3 above.
5. Her dramatic response to β-adrenergic blockade may indicate that she has had a strong β-adrenergic drive, also strengthening the β-adrenergic concept.

Prevalence of hypoglyemic fits in pheochromocytoma patients.

Symptoms of hypoglycemia and of typical pheochromocytoma attacks are similar, both being adrenergic. Therefore hypoglycemic attacks in pheochromocytoma patients may be underdiagnosed.

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