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SHORT REPORTS

Androgen production in a patient with Klinefelter's syndrome and choriocarcinoma

An association has been reported between extratesticular choriocarcinoma and Klinefelter's syndrome,[1] and the occurrence of a tumour secreting human chorionic gonadotrophin (HCG) has allowed us to study the effects of long-term HCG stimulation on the XXY aneuploid testis.

Case report

A 19-year-old sawmill worker developed a cough and haemoptysis. His shaving frequency, up to then twice weekly, became daily. His family had noticed increased hirsutism and weight loss during the preceding three months. A chest radiograph showed multiple nodular lesions 1-5 cm in diameter in both lung fields, and he required ventilation within 24 hours of admission to hospital. On examination there was striking hirsuties, smooth firm testes (2 ml each), a normal sized penis with hypospadias, and gynaecomastia. His arm span was 180 cm and crown-heel height 168 cm. A karyotype confirmed Klinefelter's syndrome; 47 XXY in all cells. An open-lung biopsy led to the diagnosis of disseminated choriocarcinoma, primary site unknown, and he was given an initial bolus comprising actinomycin C 1 mg, cyclophosphamide 1·5 g, adriamycin 40 mg, and vincristine 2 mg, then two weeks later a three-day course of cis-platinum 20 mg and VP 16-213 200 mg. He made a slow but sustained recovery with intermittent treatment with cis-platinum and VP 16-213 despite an intracranial metastasis, which was successfully treated with intrathecal methotrexate and surgical removal.

On admission his serum albumin concentration was 29 g/l and total protein concentration 55 g/l. The initial HCG concentration (detected also as luteinising hormone) was 106 211 mIU/l. The follicle stimulating hormone (FSH) concentration was 2·7 U/l (normally $<7{\cdot}0$ U/l); after 100 μg luteinising hormone releasing hormone (LHRH) was given the values were 3·0 U/l after half an hour, 2·7 U/l after one hour, and 2·6 U/l after two hours. The 8 am plasma cortisol concentration was 488 nmol/l (17·7 μg/100 ml) and the midnight concentration 108 nmol/l (3·9 μg/100 ml). Urinary 24-hour total 17-oxosteroids excretion rate was 265 μmol/24 h (76·4 mg/24 h) and 17-oxogenic steroids excretion rate 55 μmol/24 h (15·8 mg/24 h). Serum oestradiol concentration was under 150 μmol/l (40·9 ng/ml; normally 50-150 μmol/l, 13·6-40·9 ng/ml), serum testosterone concentration 11·1 nmol/l (3·2 ng/ml; normally 10·9-33·4 nmol/l, 3·1-9·6 ng/ml), serum 17α-hydroxyprogesterone (17-OHP) concentration 34·0 nmol/l (11·3 ng/ml; normally <15 nmol/l, 5 ng/ml), and serum progesterone concentration 25·9 nmol/l (8·1 ng/ml; normally $<0{\cdot}8$ nmol/l, 0·3 ng/ml). Fourteen days after admission, immediately before treatment with cis-platinum, the HCG concentration was 7386 mIU/l, 17-OHP concentration 18 nmol/l (5·9 ng/ml), and testosterone concentration 1·5 nmol/l (0·4 ng/ml). Three months after admission HCG concentration had fallen to 20 mIU/l.

Comment

In our patient there was a clear history of recent virilisation with classical Klinefelter habitus. The concentrations of plasma cortisol and excretion rates of urinary oxogenic steroids indicated normal adrenal function; the increased values for urinary oxosteroids and 17-OHP, the second exclusively of testicular origin,[2] implied that the hirsutism was secondary to testicular androgen synthesis in response to HCG stimulation. The two other patients with this association of choriocarcinoma and Klinefelter's syndrome were not investigated endocrinologically but in the first, a 16-year-old, there was a normal male escutcheon but no beard growth or gynaecomastia.[3] The second, a 21-year-old, had gynaecomastia but no hirsutism.[1]

In Klinefelter's syndrome the usual endocrine abnormalities are those of primary hypogonadism with low testosterone concentrations and raised concentrations of gonadotrophins. Although this is thought to be caused by impairment of all steps of testosterone synthesis, a disproportionate increase in the concentration of the precursor steroid 17-OHP in comparison with testosterone concentrations when such patients are given HCG for three days suggests a defect in this conversion.[4] Despite long-term endogenous HCG stimulation in our patient, testosterone concentration was just within the normal range while 17-OHP concentration was over twice normal, as were the values for urinary androgen metabolites. Progesterone concentration was also strikingly raised. There therefore seems to be strong evidence that there is a rate-limiting step in the terminal stages of testosterone synthesis from 17-OHP in patients with Klinefelter's syndrome.

Patients with an HCG-secreting tumour and Klinefelter's syndrome may have a clinical appearance masking their abnormal karyotype, with normal testosterone and suppressed FSH concentrations

(which in our patient failed to rise with LHRH values). Patients with no chromosome abnormality and an HCG-secreting tumour may have gynaecomastia and an appearance in testicular specimens at biopsy that mimics Klinefelter's syndrome[1]; they too have normal testosterone values and suppressed FSH values.[5] We suggest that karyotyping should be performed on all patients with choriocarcinoma to determine the prevalence of the association of XXY aneuploidy and this tumour, since other data may be misleading.

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Hypoglycaemia in insulin-dependent diabetic drivers

The possibility of hypoglycaemia occurring in insulin-dependent diabetics while driving is well recognised,[1] and a recent case of this type prompted us to study the problem further. A 50-year-old experienced insulin-taking driver was called out suddenly just before his evening meal. His regular source of dextrose was kept in his jacket, which in his haste had been left behind in the house. Severe hypoglycaemia ensued, but fortunately he was able to stop his car without mishap.

Patients, methods, and results

We selected at random 157 insulin-dependent diabetics (age 17-65 years) from patients attending outpatient diabetic clinics in Manchester and Sheffield. Each patient was interviewed by the same person (BC). The questionnaire contained a mixture of questions designed to establish early in the interview whether the patient was a driver. A full account of each patient's symptoms of hypoglycaemia was then taken, with particular reference to premonitory symptoms. Precipitating factors such as exercise, emotion, late meals, and alcohol were identified. Patients were then asked where they kept carbohydrate in the event of hypoglycaemia occurring and whether such material was kept permanently in their vehicles. Finally, the patients were asked if they had ever experienced symptoms of hypoglycaemia while driving. No attempt was made to estimate the frequency of this event in any particular case.

In three cases (two men, one woman) it was not possible to ascertain whether carbohydrate material was kept in the vehicle. From the table it may be seen that a much higher proportion of the male diabetic population were drivers (79% of men, compared with 37% of women). Furthermore, 49% of men drivers experienced hypoglycaemia while driving, whereas only 19% of women drivers did so. The presence of any of the patient's premonitory symptoms was taken to indicate that hypoglycaemia was occurring. The table shows that over half of both men and women drivers failed to maintain a permanent energy source in their vehicles.

Patients, prevalence of hypoglycaemia while driving, and maintenance of permanent energy source in vehicle

	Men	Women	Total
Number of patients interviewed	86	71	157
No (%) of drivers	68 (79·0)	26 (36·6)	94 (59·8)
Mean (±1 SD) age of drivers	41·8±18·08	34·1±13·20	39·7±17·28
Mean (±1 SD) duration of diabetes (years)	14·8±10·69	10·3±6·32	13·5±9·88
No (%) of drivers experiencing symptoms of hypoglycaemia while driving	33 (48·5)	5 (19·2)	38 (40·4)
No (%) of drivers who keep permanent energy sources in their vehicles (91 drivers; 66 men, 25 women)	32 (48·5)	12 (48·0)	44 (48·3)

Comment

Estimates show that about 150 000 diabetics in Great Britain are potential drivers.[2] Under the Road Traffic Act 1974 diabetes is not a disqualifying disability, although it is recommended that patients requiring insulin should not drive heavy goods vehicles or public service vehicles. Hypoglycaemia may occur suddenly during driving, even in well-stabilised diabetics. Insulin is regarded as a drug under the Road Traffic Act 1962, and a driver with symptoms of hypoglycaemia may be charged with driving while under the influence of drugs. Patients must therefore be advised that if they have any early symptoms they should stop the car and move to the back seat to take their sugar, because it is illegal to be in charge of even a stationary vehicle if under the influence of a drug. Our results indicate that hypoglycaemia while driving is commoner than might be supposed; nevertheless, a more important finding may be that less than 50% of diabetic drivers keep carbohydrate material permanently in their vehicles, although the British Diabetic Association leaflet on the diabetic driver states that carbohydrate should be kept in the car. It is unsafe to depend on material carried in bags or clothes, which may easily be left behind. In addition, road conditions may be such as to prevent drivers from stopping quickly should hypoglycaemia occur. We suggest, therefore, that the education of diabetic drivers to these hazards should be undertaken by all those responsible for their medical care.

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Requests for reprints should be addressed to Dr Ward.

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Finger wrinkling after immersion in water

Wrinkling of the skin over the pulp of the fingers after prolonged immersion in water has been suggested as a test of sympathetic function.[1 2] Since autonomic fibres are carried in the peripheral nerves, by extension skin wrinkling may also be regarded as a measure of the integrity of the peripheral nerves.[3] The physiology of this normal mechanism has been reviewed by Braham *et al.*[1] The simplicity of this innocuous bedside test of autonomic function requires an assessment of its reliability.