46XY. Her basal serum concentration of testosterone was 15 nmol/l (4·33 ng/ml) and rose to 18 nmol/l (5·19 ng/ml) after HCG stimulation.

Comment

In both these girls who were genotypically male and phenotypically female the likely diagnosis is androgen insensitivity (testicular feminisation syndrome). The rise in plasma testosterone concentration after HCG stimulation excluded gonadal agenesis and any enzyme defect of testosterone biosynthesis. Androgen insensitivity, which is probably an X-linked disorder,[1] results from a failure of end-organs to respond to testosterone.[2] The uterus is absent, but normal breast development occurs in puberty if the testes are not removed: the testes should eventually be removed because of the risk of neoplasia.[3] The diagnosis is normally made during investigation for amenorrhoea or following the appearance of testes (usually as a hernia) but may not be made at all. This is the first time, so far as I know, that the diagnosis has been made in part through amniocentesis.

This case shows that the future sex of an infant cannot be predicted with certainty by amniocentesis, and this is one reason why the mother should probably not be told the sex of her child.

I am grateful to Dr Stanley Walker, department of cytogenetics at the University of Liverpool, for expert help and to Mr E Parry-Jones, consultant obstetrician at HM Stanley Hospital, for allowing me to publish details of his patient.

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Life-threatening arrhythmias and intravenous cimetidine

Animal studies have shown histamine (H2) receptors in the heart and coronary circulation, and cardiovascular complications in man have been associated with cimetidine.[1 2] We describe two cases in which life-threatening arrhythmias occurred during treatment with intravenous (IV) cimetidine.

Case reports

(1) A previously fit 48-year-old man was found on gastroscopy to have a benign antral ulcer. He had developed late-onset asthma six months previously for which he had taken 5 mg prednisolone daily. An ECG was normal. He was started on cimetidine 1 g/day by mouth but, because his pain persisted, after 48 hours cimetidine 400 mg 6-hourly was given intravenously (IV). Twenty-four hours later, five minutes after the third dose of cimetidine IV, his blood pressure fell abruptly from 120/80 to 80/60 mm Hg without evidence of haemorrhage or perforation. It gradually rose to 100/60 mm Hg over the next six hours. After the fourth dose of cimetidine he became asystolic but responded to IV isoprenaline. Over the next eight hours he had six similar episodes, the final one proving fatal. All occurred either immediately after cimetidine (one injection) or on withdrawal of isoprenaline. Plasma electrolytes and arterial blood gases were normal throughout. Frusemide, dexamethasone, flucloxacillin, and gentamicin had also been given. Necropsy showed polyarteritis nodosa, slightly atypical in that it was confined to the heart, spleen, stomach, and duodenum.

(2) A 56-year-old man with no previous history of heart disease was transferred from another hospital with anuria after the fashioning of an ileal conduit six days earlier. On admission he was clinically septicaemic and pus was obtained on abdominal paracentesis. ECG showed sinus tachycardia but was otherwise normal. Four hours later he became hypotensive and had a cardiorespiratory arrest in asystole, from which he was rapidly resuscitated. He was given cimetidine 400 mg IV to prevent gastrointestinal bleeding. Ten minutes later sinus arrest occurred. After resuscitation he remained stable for three hours, when a further dose of cimetidine IV was associated with atrial extrasystoles and then cardiorespiratory arrest. He was again resuscitated. No more cimetidine was given and there were no further arrhythmias. The patient died 14 days after admission from renal failure and pseudomonas septicaemia. There was no necropsy. Serial measurements of plasma electrolytes and arterial blood gases showed no significant abnormalities. Ampicillin, gentamicin, and frusemide were given in addition to the drugs required for resuscitation.

Comment

Both patients had other conditions that might have caused their arrhythmias, but each showed a striking temporal association with the administration of cimetidine. We can only speculate whether it played a causal role. In the isolated guinea-pig heart histamine-induced prolongation of the PR interval is probably mediated by H1 receptors located at the atrioventricular node, while H2 receptors in the myocardium are responsible for the positive inotropic and chronotopic effects of histamine.[3] The highest plasma histamine concentrations have been in patients with sepsis or after major surgery. Thus the bradycardia and atrioventricular dissociation previously described could well have resulted from cimetidine-induced H2 blockade in ill patients with high plasma concentrations of histamine.

An alternative hypothesis implicates prolactin. Cimetidine blocks dopamine as well as histamine receptors, and therefore causes prolactin release. In healthy human volunteers there was a rapid rise in serum prolactin a few minutes after an intravenous bolus of 400 mg cimetidine.[4] Interestingly, there was no such rise after an oral dose. In rats pharmacological doses of prolactin may induce arrhythmias.[5] Indeed, we have seen two patients with prolactinomas and otherwise unexplained arrhythmia. Since patients under stress already have high serum prolactin, IV cimetidine may further increase this hormone and thus may precipitate arrhythmia. Disorders of cardiac rhythm in seriously ill patients are often ascribed to rapidly changing metabolic or haemodynamic factors. IV cimetidine may complicate their management.

We thank Drs P B Cotton and L M Selby for referring the first case and Professor D K Peters for permission to report the clinical details of the second. Fuller details of the case histories are available on request from JC, to whom requests for reprints should be addressed.

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Determination of subfractions of amniotic fluid alpha-fetoprotein in diagnosing spina bifida and congenital nephrosis

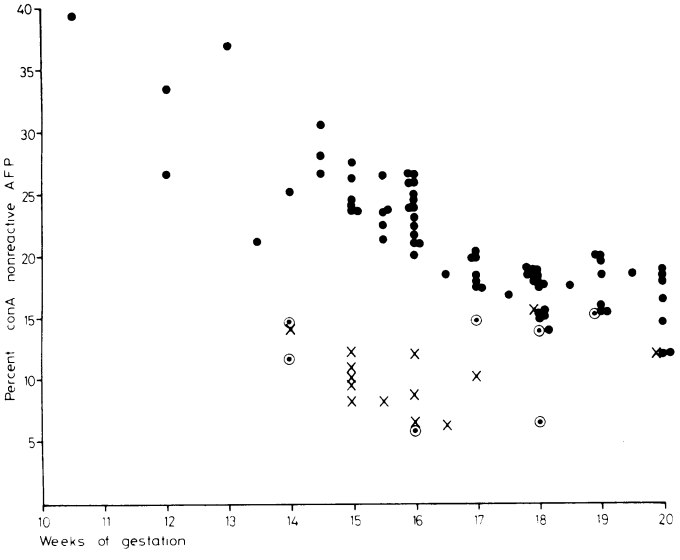
The alpha-fetoprotein (AFP) test is well established as a diagnostic tool for the early antenatal detection of neural-tube defects and congenital nephrosis. Nevertheless, this and other diagnostic measures currently available do not permit a completely accurate distinction between normal fetuses and fetuses with these malformations. We recently found that human AFP can be separated into subfractions by chromatography on concanavallin A (con A).[1] About 2-5% of fetal serum AFP does not bind to con A, and this is a constant feature throughout gestation. In contrast, 15-40% of AFP in amniotic fluid during the second trimester is non-reactive with con A. It seemed to us that the increased leakage of AFP from the fetus to the amniotic fluid associated with neural-tube defects and congenital nephrosis should not only lead to a higher concentration of AFP in amniotic fluid but could also change the relative proportions of the con A

variants. The results presented here are in agreement with this hypothesis and suggest the basis for a useful diagnostic test.

Materials, methods, and results

Out of the 95 amniotic fluid samples tested 74 were from pregnancies with a normal fetus; 14 were from cases of congenital nephrosis; four from cases of spina bifida; and three from cases of anencephaly. AFP concentrations were raised in all the 21 pathological cases. The percentage of AFP non-reactive with con A was measured by fractionating 0·1 ml amniotic fluid on a 1-ml column of con A-Sepharose (Pharmacia, Uppsala, Sweden).[1] The amount of AFP in the first 2 ml eluant obtained with the initial column buffer (the con A non-reactive fraction) was compared with the total amount of AFP applied to the column and expressed as a percentage of non-reactive AFP.

The relative amount of the AFP component non-reactive with con A in amniotic fluids from normal pregnancies decreased from 35-40% at the 11th week of gestation to about 15% at the 20th week (figure). It was lower than



Percentage of AFP non-reactive with con A in amniotic fluid samples from normal pregnancies (●) and pregnancies with congenital nephrosis (x) and neural-tube defect (⊙).

in normal pregnancies in five out of seven cases with neural-tube defects and in 12 out of 14 cases with congenital nephrosis. The cases in which the percentage of non-reactive AFP was appropriate for the normal gestational age were from the 18th, 19th, and 20th weeks of pregnancy.

Comment

AFP is produced by the yolk sac and the fetal liver,[2] and the yolk sac may be the source of the AFP non-reactive with con A. This is suggested by the finding that half of the AFP in sera from patients with yolk-sac tumours is con A non-reactive,[1] and in mice yolk-sac-derived AFP does not bind to con A while AFP originating in the liver does.[3] We hypothesise that the yolk sac contributes significantly to the AFP pool in the amniotic fluid during early gestation and that in neural-tube defects and congenital nephrosis the increased leakage from the fetus of AFP with a small non-reactive fraction changes the ratio of con A non-reactive to total AFP in the amniotic fluid. Smith *et al*[4] recently confirmed our earlier results[1] on the presence of AFP non-reactive with con A in amniotic fluid and showed that it was decreased in conditions such as spina bifida. Our present results are in general agreement with their findings, but in our hands the capacity of the test to differentiate between normal and pathological cases tended to disappear after the 18th week. That the data of Smith *et al*[4] did not show this was probably because their control cases came from the 15th to 18th week of pregnancy while most of their pathological samples were collected after the 18th week. Despite this limitation the con A test should become a useful adjunct to the regular AFP test.

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Suicide by burning—a current epidemic

Until recently suicide by burning has been unusual in Western countries. In England and Wales it accounted for less than 1% of suicides in 1963-77 and averaged only 19 cases per year. Nevertheless, between October 1978 and March 1979 there have been 42 deaths in England and Wales where a coroner has recorded the cause of death as being suicide by burning (see table). This method is not uncommon

Suicide by burning

Period	No	Period	No
1963	6	1974	22
1964	18	1975	26
1965	17	1976	22
1966	3	1977	23
1967	10	October 1978	8
1968	15	November 1978	9
1969	22	December 1978	6
1970	22	January 1979	8
1971	18	February 1979	3
1972	31	March 1979	8
1973	32		

Figures for October 1978-March 1979 exclude late notifications.

among suicide victims of Asian or African origin: in one Israeli series 77% of completed suicides among women born in Asia and Africa were by burning.[1] The same authors found that proportionately 10 times as many women as men chose this method. The current epidemic appears to date from two suicides at the beginning of October 1978. On 2 October a 24-year-old member of the Ananda Marga Sect set fire to herself on the lawn in front of the Palais de Nations in Geneva as a protest against the gaoling of the founder of the movement.[2] Two days later a London company director, aged 54, burned herself to death on the banks of the Thames at Windsor; she had been suffering from diabetes and had become depressed at the prognosis of her condition.[3]

Both suicides attracted wide publicity in the press, which persisted until November, when Dr Richard Fox of the Samaritans called for an embargo on reporting.[4] Despite an apparent response to Dr Fox's call, the numbers of these suicides has continued at an increased level.

Methods and results

Since the present epidemic became apparent the reporting coroners have been contacted for relevant details of all persons in England and Wales whose death certificates mentioned suicide or suspicious death by burning. A preliminary analysis of cases which were found to be suicide has been carried out.

Exactly half of the 42 cases were men and half women. Seven of the victims were born outside the United Kingdom. Fourteen of the 21 women but none of the 17 men of known marital state was married. Thirteen of the men and 17 of the women had a known history of psychiatric disturbance