SHORT REPORTS

Male sexual dysfunction during treatment with cimetidine

It has been suggested that the histamine H_2 -receptor antagonist cimetidine, which is widely used in the management of duodenal ulcer, should be used mainly for long-term treatment of this disease.¹ Continuous treatment with cimetidine is thought to be safe, since the documented toxicity is low. Nevertheless, we describe here three patients who developed sexual dysfunction while being treated with cimetidine.

Case reports

Case 1—A 33-year-old father of two children was treated with cimetidine (1 g/day) for four weeks for duodenal ulceration. The ulcer healed but the patient complained spontaneously that during the first week of treatment he had suffered loss of libido and thereafter had been unable to achieve erection. Within four days of discontinuing treatment his sexual function had returned to normal. Levels of luteinising hormone (LH), follicle stimulating hormone (FSH), testosterone, oestradiol, and prolactin were normal during treatment (see table).

Case 2—A 50-year-old father of four children started on a nine-month course of cimetidine (1 g/day) for duodenal ulceration. Within three weeks he suffered severe loss of libido with progression to impotence. He eventually complained after seven months of treatment, and a seminal analysis showed oligospermia. His libido has not returned during the 11 months since stopping treatment (during which he has had surgery for the ulcer). Testicular biopsy at the time of surgery (eight months later) showed active spermatogenesis in all tubules and was considered normal. FSH and prolactin concentrations were abnormal during and after treatment, while testosterone levels were towards the upper limit of normal (see table).

Case 3—A 51-year-old man started a proposed one-year course of cimetidine (1 g/day) for duodenal ulceration. When specifically questioned after 11 months the patient complained that he had noted loss of libido soon after starting treatment and that this had subsequently progressed to impotence. The symptoms did not improve after treatment was stopped. LH and FSH concentrations were raised during and after treatment (see table), though testosterone values were normal.

Hormone concentrations during and after treatment

	LH (IU/l)	FSH (IU/l)	Testos- terone (μ g/l)	Oestradiol (ng/l)	Prolactin (mIU/l)
Case 1					
On treatment	7.4	1.6	6.61	36	344
Off treatment: 1 month	12.3	5.9	5.76	20	863
Case 2					
On treatment	7.7	14.2	8.10		677
Off treatment: 3 months	9.3	11.0	7.60	7.6	520
7 months	5.5	13.6	8.90	14.7	439
Case 3					
On treatment	11.0	9.0			653
Off treatment: 4 months	11.3	9.0	8.20	33	488
8 months	15.4	13.0	8.29	44	375
Upper limit of normal*					
	7.7	7.2	9.20	40	400

*In our laboratory for patients aged over 40 years.

Comment

These three patients developed symptoms of sexual dysfunction during treatment with cimetidine, despite healing of their ulcers. Twenty-three cases of impotence (in patients aged 37 or older in whom the onset occurred from 0-7 months after treatment started) have been reported to the Committee on Safety of Medicines (personal communication) so that our patients are symptomatically not unique, although the abnormal endocrine profiles have not been previously reported. The mechanism of the loss of libido and impotence has not been defined but an endocrine basis must be suspected.²

The sexual dysfunction in our patients may be related to the abnormally high pituitary hormone concentrations. Hyperprolactinaemia in men (usually with pituitary tumours) may be associated

with sexual dysfunction,³ but the prolactin levels were not consistently raised in our patients. Cimetidine exerts an antiandrogenic effect in animals,⁴ and the abnormally high gonadotrophin concentrations, in the presence of high normal testosterone values, are compatible with an antiandrogenic effect.⁵ Preliminary studies (to be reported) indicate that gonadotrophin concentrations tend to be higher in cimetidine-treated than in untreated patients with duodenal ulcer, especially those aged over 40, so only older men may be liable to this type of reaction to cimetidine. We cannot yet explain the persistence of the abnormal gonadotrophin concentrations after discontinuing treatment in our patients, but in other (asymptomatic) individuals the high gonadotrophin values have returned to normal.

We have not proved a causal connection between cimetidine and the hormonal and sexual dysfunction of our patients. Nevertheless, because long-term administration of cimetidine seems to be useful for treating duodenal and gastric ulcers, sexual function should be monitored in these patients since our findings, together with the evidence from animal experiments, provide a *prima facie* case for such a relationship.

We thank Mr K Baxby for his helpful comments on two of these patients and Dr W H W Inman for permission to quote the reports of impotence to the Committee on Safety of Medicines.

¹ *Lancet*, 1978, **2**, 1237.

² *British Medical Journal*, 1978, **4**, 1516.

³ Franks, S, et al, *Clinical Endocrinology*, 1978, **8**, 277.

⁴ Leslie, G B, and Walker, T F, in *Cimetidine*, ed W L Burland and M A Simkins, p 24. Amsterdam, Excerpta Medica, 1977.

⁵ Neumann, F, et al, in *Androgens and Antiandrogens*, ed L Martini and M Motta, p 163. New York, Raven Press, 1977.

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Ectopic pregnancy by transmigration of sperm after sterilisation with Hulka-Clemens clips

Pregnancy after correct application of Hulka-Clemens clips is rare. We report on a case of tubal ectopic pregnancy after correctly performed sterilisation with these clips, in which fertilisation occurred after sperm transmigration.

Case Report

A 32-year-old multigravida was admitted to hospital with a four-day history of lower abdominal pain and 37 days' amenorrhoea. Eight months earlier she had been sterilised under laparoscopic vision, using Hulka-Clemens clips applied through a second incision. Ruptured ectopic pregnancy was diagnosed and laparotomy performed. A ruptured right tubal ectopic pregnancy was found lateral to the Hulka-Clemens clip on that side. Both clips seemed to be correctly placed across the isthmus portions of the tubes. A right partial salpingectomy was performed, with removal of the clip on that side.

The diagnosis of ectopic pregnancy was confirmed histologically and the clip was correctly placed across the tube. At one side of the clip the tube seemed completely obstructed, but at the other side the lumen of the tube was patent and opened into the space occupied by the clip. Although this is unusual, it is difficult to imagine how it allowed the tube to remain functionally patent. A hysterosalpingogram was performed, which showed tubal patency on the left side. A further laparotomy, and an Irving-type sterilisation were performed, and the clip was removed from the left side.

The rear end of the upper jaw surrounding the hinge of the clip was defective, and broke when the clip was opened after removal of the spring. The manufacturers (Rocket) examined the clip and confirmed that the pivot was broken. Nevertheless, they thought that this would not have made the device fail, since the pin and pivot are only mechanical contrivances to apply the clip. The spring function was within accepted limits. The clip failed in the approximation of the two jaws, but whether this was secondary failure due to distortion of the moulding after the pivot had been broken could not be determined.

Comment

Sterilisation with Hulka-Clemens clips is well established. It is relatively simple to perform, avoids the dangers of diathermy, and minimises tubal damage, which is important if reversal of sterilisation is to be considered.² Pregnancies may occur after sterilisations of all types, and after surgical division or diathermy pregnancy is usually due to formation of tuboperitoneal fistulae.³ Failure of the spring has caused failed clip sterilisation.¹ This case shows that the plastic jaws are susceptible to breakage or distortion.

Transmigration of sperm with fertilisation and implantation in the contralateral tube is another interesting feature of this case. This phenomenon has been doubted,⁴ but transmigration of sperm⁵ or ova was the only satisfactory explanation of pregnancy in three other reported cases. If tubal pregnancy follows any sterilisation procedure both Fallopian tubes should be considered as possibly patent and so religated, preferably by the Irving technique, which has the lowest failure rate³ of methods of tubal sterilisation.

¹ Hulka, J F, *et al*, *Fertility and Sterility*, 1975, **26**, 1122.

² Lieberman, B A, *et al*, *Journal of Reproductive Medicine*, 1977, **18**, 241.

³ Garb, A E, *Obstetrical and Gynecological Survey*, 1957, **12**, 291.

⁴ Jeffcoate, N, *Principles of Gynaecology*, 4th edn, p 215. London, Butterworths, 1975.

⁵ Cortes, P J, *Acta Ginecológica*, 1972, **23**, 671.

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Dermatoglyphics in children with febrile convulsions

It is widely accepted that dermatoglyphics are inherited in a polygenic manner¹ and that the final dermatoglyphic pattern is set by about the 19th week of gestation.² Any environmental factor accounting for an increased familial prevalence of dermatoglyphic abnormalities must therefore operate in early intrauterine life. The presence of dermatoglyphic abnormalities in children with febrile convulsions and in their parents would indicate the presence of genetic factors and possibly shed new light on the genetic mechanisms. This is the first report of such an investigation.

Subjects, methods, and results

The dermatoglyphics of 513 Chinese parents and children were studied. They comprised 400 schoolchildren (200 boys and 200 girls) who served as controls; 76 children with febrile convulsions admitted to the university department of paediatrics (54 with up to four episodes recorded, and 22 with more than four episodes recorded, often with afebrile seizures as well); and 37 parents of children with febrile convulsions. Patterns in the thenar and first to fourth interdigital areas were classified as proposed by Plato and Wertecki,³ except that in the fourth interdigital area only unusual patterns were studied (patterns coded 0-4 were excluded).

The children with up to four episodes of febrile convulsions showed increased prevalences of several patterns (see table). A pattern was present in the third interdigital area in 16 (29.6%) of these children compared with 66 (16.5%) of the controls ($P < 0.05$); in 14 cases the pattern was a radial loop. Unusual patterns in the fourth interdigital area were found in 11 (20.4%) of

Percentage prevalences of dermatoglyphic patterns in subjects studied

	Controls (n = 400)	Group with febrile convulsions		
		Children with ≤ 4 episodes (n = 54)	Children with > 4 episodes (n = 22)	Parents (n = 37)
Fingertip patterns				
Whorls	40.2	42.0	44.5	43.2
Ulnar loops	54.4	54.5	50.9	53.3
Radial loops	3.4	2.4	3.2	2.4
Arches	2.0	1.1	1.4	1.1
Palmar dermatoglyphics				
Thenar/1st interdigital area, presence of pattern	0	1.9	0	0
2nd interdigital area, presence of pattern	3.0	3.7	4.5	0
3rd interdigital area:				
Presence of pattern	16.5	29.6*	13.6	32.4*
Radial loop	15.5	25.9	13.6	29.7
4th interdigital area:				
Presence of unusual pattern	5.8	20.4**	9.1	8.1
Radial/accessory loop	3.8	16.7*	9.1	5.4
Accessory triradius	1.3	3.7	0	2.7
Hypothenar area:				
Presence of pattern	13.5	7.4	4.5	29.7*
Radial loop	9.5	5.6	4.5	18.9
Absence of c triradius	13.0	13.0	4.5	10.8
Accessory t triradius	1.3	0	0	8.1
Distal t triradius ($\geq 30\%$ palmar height)	6.0	5.6	9.1	18.9*
Simian crease	9.8	13.0	36.4*	16.2
Sydney crease	2.0	9.3	4.5	5.4
Bilateral distal border termination of distal transverse crease	12.5	29.6**	13.6	13.5
Radial border termination of thenar crease	8.3	13.0	13.6	16.2

Significance of difference from controls: * $P < 0.05$; ** $P < 0.01$.

the children with up to four episodes but in only 23 (5.8%) of the controls ($P < 0.01$). The radial/accessory loop was the most common pattern (nine patients (16.7%) compared with 15 (3.8%) of the controls; $P < 0.05$). Bilateral distal border termination of the distal transverse crease was present in 16 (29.6%) of the children with up to four episodes compared with 50 (12.5%) of the controls ($P < 0.01$). The only abnormality found in the children with more than four episodes of febrile convulsions was a greater prevalence of the simian crease than in the controls (eight cases (36.4%) compared with 39 (9.8%); P close to 0.01).

The parents of the children with febrile convulsions also showed a greater prevalence of a pattern in the third interdigital area (12 cases (32.4%)) than the controls (66 cases (16.5%)) ($P < 0.05$). Again the most common pattern was the radial loop (11 cases). Two unexpected dermatoglyphic abnormalities were also found—namely, an increased prevalence of a pattern in the hypothenar area (11 cases (29.7%) compared with 54 (13.5%) among the controls; $P < 0.05$), in most cases (7) the pattern being a radial loop; and an increased prevalence of distal location of the axial t triradius (30% or more of palmar height) (seven cases (18.9%) compared with 24 (6%) among the controls; $P < 0.05$).

Comment

The significantly increased prevalence of dermatoglyphic abnormalities in children with febrile convulsions and in their parents suggests a polygenic mode of inheritance. Thus the view that febrile convulsions are inherited by a single dominant gene with incomplete penetrance⁴ needs to be re-examined. The difference in dermatoglyphic patterns between children with up to four and more than four episodes of febrile convulsions (often with afebrile seizures as well) suggests that there are two types of febrile convulsions—namely, non-epileptic and epileptic. This is supported by recent work on the oculocardiac reflex in febrile convulsions.⁵ The view that most febrile convulsions have epileptic mechanisms also needs to be re-examined.

Further work on the dermatoglyphics of children with febrile convulsions may well result in a clinical method of distinguishing non-epileptic from epileptic varieties.

¹ Schaumann, B, and Alter, M, *Dermatoglyphics in Medical Disorders*. New York, Springer-Verlag, 1976.

² Mulvihill, J A, and Smith, D W, *Journal of Pediatrics*, 1969, **75**, 579.

³ Plato, C C, and Wertecki, W, *American Journal of Physical Anthropology*, 1972, **37**, 97.

⁴ Frantzen, E, *et al*, *Neurology*, 1970, **20**, 909.

⁵ Stephenson, J B P, *British Medical Journal*, 1978, **2**, 726.

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