attention paid to plasma sodium concentrations and urine output.

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Coexistence of hereditary angioedema and Turner's syndrome

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Summary

A 34-year-old woman presented to the out-patient clinic with angioedema and type II hereditary angioedema was confirmed immunologically. She also volunteered she had never had a menstrual period and physical examination identified several features of Turner's syndrome. A mosaic karyotype with XY and XO was found on chromosomal analysis and gonadectomy was performed in view of the high risk of gonadoblastoma. After commencing oestrogen at physiological replacement doses, the patient experienced a marked deterioration in both the severity and frequency of angioedema attacks. Coexistence of hereditary angioedema and Turner's syndrome has not previously been reported and this case highlights the detrimental C1 inhibitor level lowering effect of oestrogen in hereditary angioedema.

Keywords: hereditary angioedema; Turner's syndrome; oestrogen therapy

A 34-year-old woman presented with several attacks of an acutely swollen tongue and abdominal pains. She was treated initially with chlorpheniramine and prednisolone and made a good recovery. The diagnosis of hereditary angioedema type II was made on finding reduced plasma C4, normal C1 inhibitor and absent C1 inhibitor function: C3 0.93 g/l (normal range 0.75-1.65), C4 0.04 g/l, (0.20-0.65), C1 inhibitor 0.33 g/l (0.15-0.35); C1 inhibitor function was unmeasurable (normal range 40-150 units/ml). There was no family history of hereditary angioedema. Furthermore, at her initial presentation, she stated that she had never had a menstrual period and on examination had features of Turner's syndrome

with short stature, wide carrying angle and a webbed neck (cardiovascular examination was normal). Subsequent chromosomal analysis showed a mosaic karyotype consisting of one cell line with monosomy X and a second cell line with a 46 XY component. Serum oestradiol was undetectable and gonadotropin levels were raised (follicle-stimulating hormone 53.8 IU/l (<21), luteinising hormone 21.8 IU/l (<57)).

The patient was given tranexamic acid as prophylaxis for attacks which occurred with a maximum frequency of one every six weeks, but she obtained little benefit. Gonadectomy was advised because of the risk of developing gonadoblastoma¹ and hormone replacement therapy was withheld until the operation had been performed. Two streak ovaries were removed laparoscopically and there was no histological evidence of malignancy.

Postoperatively, hormone replacement therapy was commenced with combined conjugated oestrogen (625 µg) and progesterone but within six weeks, the patient experienced a three- to four-fold increase in the frequency of her attacks of angioedema to one attack every 10-14 days. The attacks were more severe and lasted on average two hours longer. Treatment with danazol (following discontinuation of tranexamic acid) was introduced at a dose of 200 mg daily and complete remission was induced (currently for six months). There have been no abnormalities in liver function tests.

Discussion

Hereditary angioedema is an autosomal dominant disease due to mutations within the C1 inhibitor gene. This leads to plasma deficiency of C1 inhibitor and allows the auto-activation of C1 and consumption of C2 and C4. There are two phenotypic variants: type I is characterised

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by low antigenic and functional plasma levels of a normal C1 inhibitor protein. Type II is characterised by the presence of normal or elevated antigenic levels of a dysfunctional or mutant protein together with a reduced level of functional protein.²

Women taking oestrogens have low levels of plasma C1 inhibitor.³ Oestrogens are therefore contraindicated in hereditary angioedema, as their usage may lead to a worsening of attacks. Our patient, who was oestrogen deficient because of her Turner's syndrome, experienced marked worsening of angioedema attacks when she received oestrogen replacement to physiological levels.

The coexistence of Turner's syndrome and hereditary angioedema has not previously been described and we hypothesise that the angioedema would have declared itself at a younger age in our patient if she had had normal oestradiol production from normal ovaries. In a recent review of 226 patients with hereditary angioedema, only 1% presented at age greater than 30 years.²

There are three arms to treatment: long-term and short-term prophylaxis, and treat-

Learning points

- oestrogen treatment, even at physiological replacement doses, worsens attacks in hereditary angioedema
- attenuated androgen treatment with danazol reverses this effect

Box 2

ment of acute attacks. Attenuated androgens such as danazol are used for prophylaxis and their precise mechanism of action is not known. There has been a report that hypogonadism or anti-androgen treatment may also result in attacks of angioedema.⁴ It has been suggested that attenuated androgens increase the hepatic synthesis of C1 inhibitor, but some patients who obtain benefit from danazol do not have a corresponding rise in plasma C1 inhibitor concentration.⁵ Hazards of long-term treatment include virilisation, increase in low-density lipoprotein cholesterol and a reported association with the development of hepatic neoplasia.⁶ The use of danazol is usually reserved for those patients who have more than one angioedema attack per month. Other prophylactic treatment includes tranexamic acid and ϵ -amino caproic acid. Acute attacks are best treated early with tranexamic acid (1 g, 3–4 hourly). Metoclopramide and antispasmodics may be helpful. C1 inhibitor therapy has recently been shown to be highly effective at terminating acute attacks,⁷ but at the present time C1 inhibitor concentrate is not covered by a product licence in the UK.

In conclusion, the highly unusual co-incidence of Turner's syndrome in a patient with hereditary angioedema highlights the deleterious effects of oestrogens in the latter condition, even when given in physiological replacement doses. Treatment with attenuated androgens such as danazol reverses this effect.

Features of hereditary angioedema

- autosomal dominant inheritance
- recurrent attacks of subcutaneous swelling and abdominal pain
- low plasma levels of functional C1 inhibitor
- autoactivation of C1 and consumption of C2 and C4
- two phenotypic variants: type I: low functional levels of normal C1 inhibitor protein; type II: normal or elevated levels of dysfunctional C1 inhibitor protein with low levels of functional protein

Box 1

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