SPONTANEOUS REMISSION IN THE AHUMADA — DEL CASTILLO SYNDROME

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The association of spontaneous galactorrhoea with primary or secondary amenorrhoea is a striking clinical picture and has increasingly engaged the attention of clinicians as, during the past two decades, numerous and diverse etiological factors have been incriminated. Much stress has been laid in the past on the persistence and intractibility of symptoms in patients belonging to the group originally described by Ahumada and del Castillo (1932), and later by Argonz and del Castillo (1953). It is only natural to expect reversion to normality when an offending factor, such as a drug, is withdrawn. A case is described below where no known causative factors were present. The clinical picture showed spontaneous remission thereby giving rise to the implication that a reversible functional disturbance may exist in such cases.

Case Report

A 30-year old nulliparous woman, R.F., who had been married 11 years, was referred to hospital on 14/11/67 as a case of "acute glomerulonephritis". She had developed that day left flank ache. Her urine had become scanty and was brown in colour, and she had a temperature of 100°F. She had suffered an attack of sore throat about three weeks previously. She gave a history of recurrent attacks of tonsillitis but had never suffered from kidney trouble before. Puffiness of the face and legs had appeared over the past two days.

The patient gave a history of six months amenorrhoea and said she had noticed spontaneous ejection of milky fluid from the breasts in the latter three months. She did not give a history of headaches or episodes of unconsciousness.

Examination on admission revealed an obese woman in fairly good general condition with a puffy face. There was no acne or excessive hirsutism. She had a temperature of 100°F., a pulse of 120 beats/min., a B.P. of 120/70 mm. Hg, and a respiratory rate of 28/min. The tonsils were enlarged and inflamed. The kidneys were not palpable. Pitting oedema in the legs was present. No abnormality was detected on neurological examination.

Investigations included: Heamoglobin level - 13.6 Gms./100ml (98%); WBC - 14000/c. mm. and a PCV of 46%. Urine output per 24 hrs. varied from 100 to 300 cc. in the first few days. The urine was dark and there was massive proteinuria together with microscopic haematuria and numerous granular casts. The initial blood urea level was 92 mgms/100ml. Serum electrolytes were: Na 142 mEq./litre, K 4.7mEq./litre, and plasma chlorides 99mEq./Litre. β-haemolytic streptococci were cultured from the patient's throat and her initial anti-streptolysin-O titre was 333 Todd units rising to 625 units four weeks later.

The patient's electrocardiogram was essentially normal. Other investigations include: Serum calcium 5.3mEq./litre and plasma inorganic phosphates 3.2mgms./100ml. A glucose tolerance test showed a fasting level of 78mgms./100ml rising to a peak level of 124mgms/100ml in one hour and falling to 93mgms./100ml at the end of two hours. X-rays of the skull showed no abnormality and the pituitary

fossa was normal. Fundoscopy and fields of vision were normal. The haemagglutination-inhibition test for pregnancy was repeatedly negative.

Over the next few days her general condition deteriorated. Oedema became more marked. Her sedimentation rate, which was 22mm in the 1st hour (Westergren method) on admission, rose to 65mm/1st hour. Her B.P. reached a peak of 200/145mm Hg, and her blood urea went up to 248mgms/100ml.

The patient was started on Ansolysen injections every few hours and; later, on magnesium sulphate enemas. Her urine output slowly increased, her blood pressure returned to normal and her general condition improved over the next two weeks. Her blood urea fell to near normal limits.

As she was now convalescent as far as her kidney lesion was concerned, it was decided to pay more attention to the interesting combination of galactorrhoea and amenorrhoea which preceded her acute illness by a few months. She was adamant on questioning that she had not taken any psychotropic drugs, anovulatory steroids or any other form of medication. There had been no severe emotional stress during the previous year. The patient had, however, had a weight increase of one and a half stone during the preceding six months.

Further investigations were undertaken. Analysis of the milky fluid expressed from the breasts showed a pH of 7.0, a relatively high fat content and lactose. 17-ketosteroids and glucocorticoids were 7.0/mgms and 11.8 mgms per 24hrs respectively, i.e. within normal limits. Gynaecological examination under anaesthesia, and dilatation and curettage (Prof. A. P. Camilleri) showed a small, retroverted uterus with a cavity of $2\frac{1}{2}$ins, a palpable, not enlarged right ovary, and scanty curettings. Histological examination of the latter showed a proliferative non-secretory endometrium (Prof. G. P. Xuereb). The patient was well enough to be discharged from hospital on 22/2/68, fourteen weeks after admission.

In early May 1968 galactorrhoea stopped and regular menstruation restarted. As it was not possible to estimate urinary gonadotrophin levels at the time of her hospital stay, these were estimated in late May 1968, when she started to recover. The F.S.H. levels were then at very low limits of normal.

Discussion

The combination of galactorrhoea and amenorrhoea, together with the development of obesity in a nulliparous woman, are the striking features of this case.

Review of the literature shows numerous and very varied causes that have been incriminated over the years. These include psychiatric causes (Giraud, 1961), and intracranial pathological conditions at a number of sites especially those affecting the hypothalamo-hypophyseal region. An eosinophilic adenoma causing acromegaly is a well known cause of galactorrhoea. Other types of pituitary tumours, including chromophobe adenomas and craniopharyngiomas have been implicated (Linquette, *et al.* 1961; Forbes, *et al.* 1954), as well as pineal tumours (Oestreich and Slawyk, 1899). Other diverse intracranial pathological causes have included the odd case after brain trauma, encephalitis, and T.B. meningitis (Ravera, *et al.* 1961).

An interesting group appear related to increased afferent stimulation of the chest wall following thoracotomy, herpes zoster lesions, and burns. Drugs as an aetiological cause have recently loomed into one of the most important causes of galactorrhea. Reserpine (Somlyo and Waye, 1960), chlorpromazine and other phenothiazine derivatives (Robinson, 1957) are especially important. It has been estimated by Robinson (1957) that there is a 10% incidence of galactorrhoea in all female patients receiving chlorpromazine. If the daily dose exceeds 300/mgms then the incidence rises to 30%. Other psychotropic drugs incriminated include imipramine (Klein, *et al.* 1964), prochlorperazine and meprobamate (Hooper, *et al.* 1961). Hypotensive drugs such as alpha-methyl dopa have been

described as a cause (Pettinger, *et al.* 1963).

Particular interest has centered round the groups described where the etiological factor is unknown, and where a number of clinical features may be present. Persistent lactation following a recent pregnancy and associated with amenorrhoea, hypogenitalism, malnutrition and psychiatric disorder are usually grouped together under the term Chiari-Frommel syndrome.

Del Castillo, in a series of papers, described another group occurring usually in nulliparous women and accompanied by amenorrhoea, evidence of oestrogenic insufficiency, and low urinary gonadotrophins (Ahumada and del Castillo, 1932; Argonz and del Castillo, 1953). Three of the four cases described in 1953 were nulliparous women while one, Case No. 3, had had a pregnancy nine years previously. One of their cases had primary amenordhoea while the other three had secondary amenorrhea. These authors felt that their cases, though related to adenohypophyseal eosinophilic cell dysfunction were distinct from those described associated with clinical acromegaly (del Castillo and Lanari, 1933). Though Argonz and del Castillo felt that the syndrome they described was similar to that described by Forbes, Henneman, Grisewold and Albright (1951), the modern tendency is to separate them, and to group under the Forbes Albright heading those cases which show enlargement of the sella turcica or evidence of a pituitary tumour, such as a chromophobe adenoma, so long as there is no evidence of acromegaly. In eight of the fifteen cases described by Forbes *et al.* (1951) a pituitary tumour was present.

Our patient's clinical picture coincides with the group often known as belonging to the Ahumada-del Castillo or the Argonz-del Castillo syndrome. We feel it is more correct to refer to the syndrome as the Ahumada del Castillo syndrome rather than the Argonz del Castillo syndrome as the former two workers described it as early as 1932.

The urinary gonadotrophin levels obtained in this case can only be interpreted in the light of the clinical manifestations, and they probably reflect urinary gonadotrophins which were returning to normal. It is most interesting to note that in spite of the original claims by del Castillo *et al*, and Forbes *et al*, that urinary gonadotrophins are low, it is the view of experienced workers such as Peake and Daughaday (1968) that low urinary gonadotrophin excretion has been an inconsistent finding in patients clinically similar to those described by del Castillo and his coworkers in all other respects, and that, therefore, a low urinary gonadotrophin level is not necessary for the completion of the syndrome.

The mechanisms underlying abnormal lacatation are obscure and various theories have been proposed in the past to explain the mechanism of non-puerperal lactation. Three of the main theories advocated have been those of Nelson (1936), Meites and Turner (1942), and Folley (1956).

It is nowadays thought, however, that the all-important factor is the hypothalamus which appears to exert a restraining influence on the liberation of prolactin by the pituitary. The neuroendocrinal function of the hypothalamus in inhibiting the liberation of prolactin from the pituitary was demonstrated by Eckles and his co-workers (1958), who noted the development of persistent lactation in women with carcinoma of the breast who underwent pituitary stalk section and the insertion of a polyethylene plate between the cut ends.

It now appears that the active factors are protein or polypeptide substances of relatively low molecular weight secreted by certain parts of the hypothalamus, particularly the median eminence, and transported to the adenohypophysis where they regulate the secretion of each of the adenohypophyseal hormones. These substances may either stimulate or inhibit pituitary hormone release. The substance governing pituitary prolactin liberation is known as the luteotrophic inhibitory factor as its presence appears to diminish or suppress lactation (Achally, *et al.* 1964;

Guillemain, 1967). Hence the different syndromes mentioned above may all result from hypothalamic dysfunction causing diminution of pituitary prolactin liberation.

It should be emphasised that the usual methods of gonadotrophin assay by the mouse uterine weight method are not pure FSH determinations but measure also some luteinising hormone (LH) and luteotropic hormone (LTH) activity as well. The surprise finding in our case of a proliferative endometrium when the patient still had galactorrhoea would indicate that FSH production was not, at that time, impaired, and may imply that this endometrial proliferation was a new phenomenon and the first indication of an impending recovery. The finding of an abnormally small uterus with a uterine cavity of $2\frac{1}{2}$ ins. is consistent with longstanding low levels of oestrogens and progesterone which, in this case, would be the result of low gonadotrophic hormone secretion.

It is important to note in this respect that the use of parenteral medoxyprogesterone acetate in doses capable of inhibiting gonadotrophic hormone in patients with sexual precocity was found to be ineffective in the suppression of lactation associated with either the Chiari Frommel or Forbes Albright syndrome. Thus the inhibition of one component of the gonadotrophic triad (i.e. FSH) does not necessarily mean suppression of other units of the complex (i.e. LTH) (Kuppermann, 1967).

It was not possible to carry out a therapeutic trial in our case with clomiphene citrate (an analogue of the non-steroidal oestrogen chlortrianserine). In some cases of the Chiari Frommel syndrome it has been used with success (Kasen, 1963), as also in some cases of the Ahumada del Castillo syndrome (Whitelow, 1966). In other patients suffering from the latter syndrome, however, no beneficial results have been seen (Kempers, *et al.* 1967).

Had clomiphene been administered to our patient towards the end of her illness, the spontaneous remission that occurred could easily have been attributed to the drug. The potential coincidence between spontaneous remission and clomiphene administration must be borne in mind when assessing the benefits of clomiphene in patients with this syndrome.

Perusal of the literature on the subject shows insufficient data regarding the long term follow up of a significant number of the cases described. It is reasonable to suppose that some of these cases represented varying degrees of hormonal disturbance. It would not be a surprise to find that some of the cases with minimal dysfunction may have shown a spontaneous cessation of the galactorrhoea and amenorrhoea after an interval of time.

In the absence of a space occupying or progressive lesion, it may be postulated that a reversible functional disturbance occurred in the present case. There seems to be no reason why there should not be, on occasions, remissions in some of these cases. In our case the patient stopped lactating spontaneously shortly after her acute renal illness. One can rule out that this was solely due to the stopping of hypotensive drugs as the galactorrhoea and amenorrhoea antedated by months the use of any drug. One wonders whether the patient's renal illness affected her hypothalamic dysfunction.

The causal factors underlying the hormonal disurbance in the third case described by Argonz and del Castillo (1953) would appear to have been acquired as their patient had been endocrinologically normal before and had had a normal pregnancy nine years previously.

It is the purpose of this paper to point out that the syndrome of idiopathic galactorrhoea and amenorrhoea need not necessarily have a poor therapeutic prognosis but may show spontaneous remission.

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