Institute of General Medical Clinic and Medical Therapy,
and Institute of Endocrinology and Constitutional Medicine, University of Florence, Italy

STEIN-LEVENTHAL SYNDROME IN SISTERS

The Possible Role of Genetic Factors in the "Polycystic Ovary Syndrome"

A. BORGHI, M. MAIELLO, G. GIUSTI

SUMMARY

Two pairs of sisters are reported who showed clinical, morphologic, and hormone abnormalities, such as to be classified in the picture of the so-called Stein-Leventhal syndrome.

These cases, as other few similar observations, may suggest the possibility that, at least in some instances, the Stein-Leventhal syndrome can be governed by factors of a genetic order.

After a short review of the literature on this subject, it is pointed out that enough evidence supports the existence of *predisposing* genetic factors to the manifestation of the syndrome, although a true heredity of the disease cannot at the moment be entirely supported. Also some fraternal cases could find an explanation in lesional actions repeated during subsequent pregnancies.

The "Stein-Leventhal syndrome" indicates a clinical and anatomical picture with extremely vague outlines. It has been discussed for years now without reaching any certain and generally accepted conclusions.

According to the prevalent opinion, the Stein-Leventhal syndrome is essentially characterized, on clinical grounds, by sterility and menstrual abnormality (generally constituted by oligomenorrhea or secondary amenorrhea), often associated with more or less evident signs of hyperandrogenism; and on morphologic grounds by bilaterally enlarged ovaries, with hyperplastic fibrosis of the cortical stroma, polycystosis with thecal hyperplasia, congestion, and stromal oedema. While according to some authors this syndrome constitutes a well-defined entity, others have their doubts about its existence, and others consider it to be just a transient aspect of a progressive alteration of the ovary which would begin with simple microcystic degeneration, leading to hyperthecosis with diffused luteinization (Geist and Gaines's ovary).

Numerous hypotheses have been formulated with regard to the pathogenesis of the disease, which is even now substantially unknown. The only point which now seems to be definitely clear is that a deficit of the conversion to estrogens of the C-19-oxygenated ovarian steroids, in affected subjects, exists, with a consequent increase of ovarian androgens (Lanthier and Sandor 1960, Axelrod and Goldzieher 1962, Mahesh and Greenblatt 1962, etc.). It is not clear whether this enzyme defect is linked to primitive ovarian abnormalities or to other endocrine abnormalities (and to extraendocrine pathology). However, some observations suggest the possibility that, at least in some cases, this can be governed by factors of a genetic order.

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During the last few years we have had the opportunity of studying two pairs of sisters who showed such clinical, morphologic, and hormonal abnormalities, that we were able to classify them in the ambit of the Stein-Leventhal syndrome. The publication of a contribution by Cooper et al. (1968) on the " hereditary factors in the Stein-Leventhal syndrome " has prompted us to point out the cases which we have studied and to reconsider the possible role of the above-mentioned factors in the genesis of this syndrome.

CASE REPORTS

Family R.

The father died young, in war. The mother, aged 51 and in good health, had regular menstrual cycles until the age of 49 when she began the menopause quite normally. She only had two pregnancies from which the two patients examined by us were born. The mother and maternal grand-mother had mild hypertrichosis on the upper lip.

ANNA (FIRST-BORN)

Admitted to hospital in May 1961 at the age of 22.

Born naturally but in the 7th month of pregnancy whith serious phenomena of toxaemia. Breast-fed. First physiological functions normal.

Menarche at 12. Menstruation was regular in cycle, quantity, and length until the age of 18. Since then it has become heavier and heavier, so much so that the patient was admitted to the gynecological ward for serious posthemorrhagic anemia. During that period she was also treated with strong doses of male hormones.

For about a year now the menstrual cycles have been very irregular, notably heavy and long-lasting (even 20-30 days.) At the time when she was admitted to hospital, the patient had been suffering with menorrhagia for about 2 months.

Since the menarche, the patient has had hirsutism which increased notably after administration of androgens, and which is developing even now.

LUCIANA (SECOND-BORN)

Admitted to hospital in October 1965 at the age of 23.

Born naturally at the 9th month after pregnancy whith phenomena of toxaemia. Breast-fed. First physiological functions normal.

Menarche at 10. Menstruation was regular for 4 years, but very heavy, and lasted 6 days. At the age of 14 the patient had two cycles close together, after which amenorrhea set in, still persisting now. Every 3-4 months the patient has an injection of an oestrogen-progesterone association, which is followed, after about 15 days, by a moderate menstrual cycle.

During the months in which she does not have this injection, the menstrual cycle does not appear, but the patient notices regular menstrual symptoms such as abdominal pains and headache.

Contemporary to the cessation of the menstrual cycles (at 14), hirsutism, which is still developing, appeared together with loss of hair and progressive obesity.

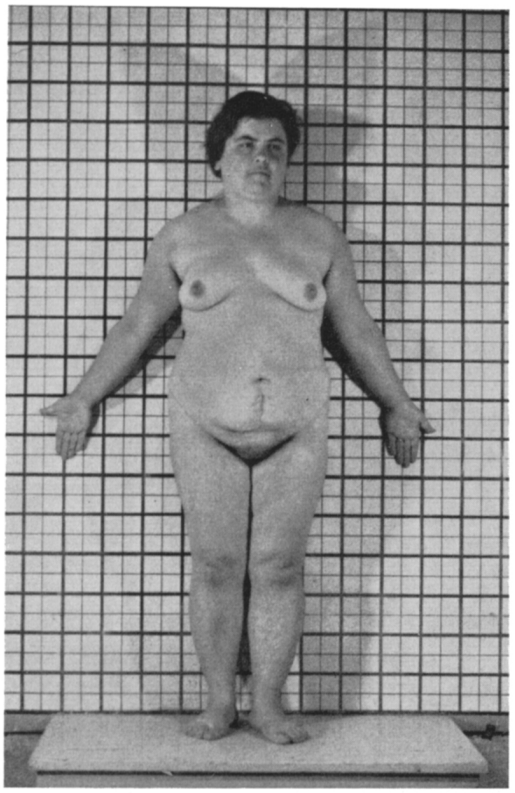

FIG. 1*a*. Anna R. at age 29

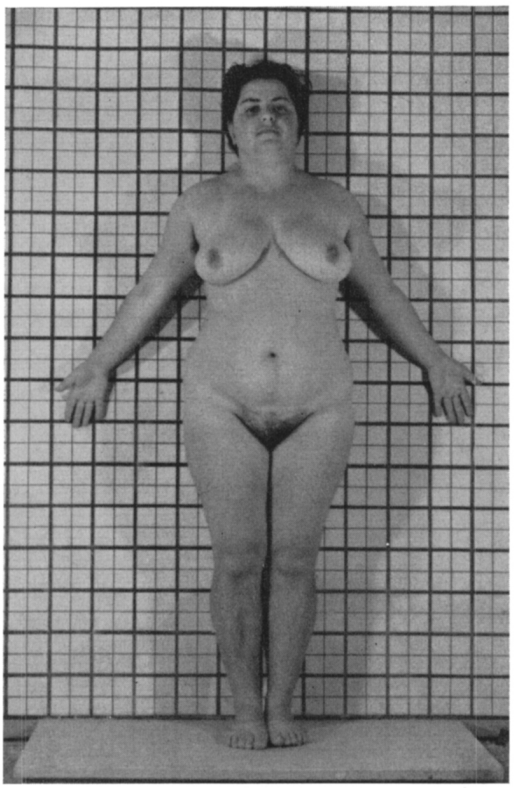

FIG. 1*b*. Luciana R. at age 23

Contemporary to the beginning of menstrual abnormality (at 18), the patient began to show signs of frontal headache and bulimy, which has led to an increase in weight of over 14 Kg in 2 years.

Physical Examination

Short in stature with diffused obesity of android type. Height 154 cm, weight 79 Kg.

Prevalent physical development of the trunk over the limbs, of which the upper segments are almost as long as the lower segments.

The patient has suffered from frontal headache since the age of 14.

Physical Examination

Short in stature with diffused obesity of intermediate type. Height 155 cm, weight 73.5 Kg.

Prevalent physical development of the trunk over the limbs, of which the upper segments are almost as long as the lower segments.

Skin and visible mucosae well sanguified. Oily skin.

Hirsutism evident on the face (upper lip and chin), on the lower limbs, infraumbilical line and breast region. The hairs are not very numerous, but thickish and hyperpigmented.

Acne on the face and back.

Well developed breast but with only modest glandular components. Normal external genitalia.

Common laboratory tests: within normal limits.
B.M. + 7%.

Cranial X-ray: small sella, with narrow aditus.

Pneumopelvigraphy: uterus larger than normal; ovaries noticeably large (especially the right ovary), globose, with regular curves (Fig. 2*a*).

Skin and visible mucosae well sanguified. Quite oily skin.

Hirsutism all over the face (upper lip and region below the chin), and on the lower limbs and breast region.

Acne on the face and back.

Large breasts with an apparently fairly developed glandular component. Normal external genitalia.

Common laboratory tests: within normal limits.
B.M. + 15%. P.B.I. 7.2% g.u.

Uptake, I 131. Maximum thyroid uptake (at 24th hour), 33.6%. Halved uptake time, 10 days.

Cranial X-ray: no particular observation.

Pneumopelvigraphy: small uterus; very large ovaries, the left ovary being date-shaped and the right increased in all its diameters (Fig. 2*b*).

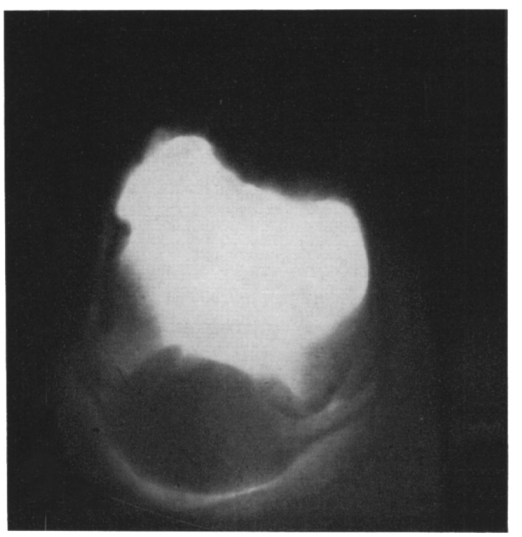

FIG. 2*a*

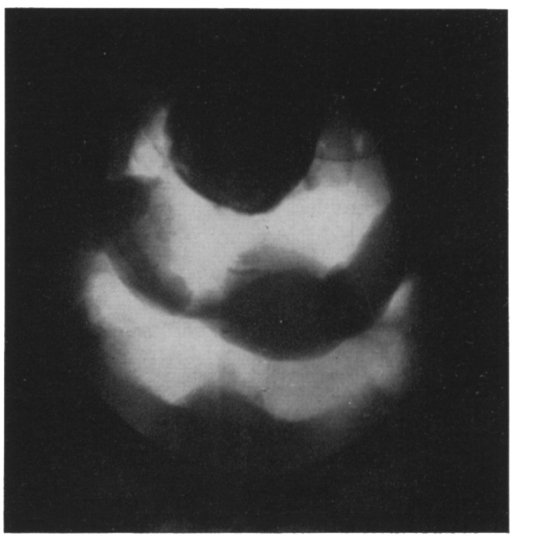

FIG. 2*b*

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HORMONE TESTS [1]

Treatment	17-KS (mg)	17-OHCS (mg)	Phenolst. (μg)	Treatment	17-KS (mg)	17-OHCS (mg)	Phenolst. (μg)	FSH (R.U.)
None	6.1	3.6	20.2	None	4.2	3.9	28.4	
After Δ FF	4.1			After Δ FF	5.7	1.1		
Reacthin 20 U.	5.8	6.4		None	7.2	4.6		4.5
Reacthin 20 U.	7.5	8.6		ACTH 40 U. (e. v.)	9.8	11.2		
Reacthin 20 U.	4.8	12.8						

Transferred to the surgical ward with the diagnosis of Stein-Leventhal's syndrome, (metrorrhagic type), and operated on the 8.VI.61 (bilateral wedge resection of the ovaries).

Surgical Findings

Ovaries entirely increased in size (the right ovary more than the left), with stretched, smooth surface of a white, mother-of-pearl colour, under which numerous cysts of a maximum diameter of 7-8 mm are visible. The organ is hard to the cut and does not bleed much.

Histological Examination

Evident collagenization of the outer stroma. The primordial follicles are quite numerous and well-preserved. No sign of evolutive follicles. The cystic formations have a univocal structure. The granulosa is still well represented in their wall; this appears as a thin, continuous layer, quite well developed, while the theca, in which

Plasma cortisol: basic, 12.1% μg; after four hours ACTH e.v., 40.2% μg.

Transferred to the surgical ward with the diagnosis of Stein-Leventhal's syndrome and operated on 9.XI.65 (bilateral wedge resection of the ovaries).

Surgical Findings

Ovaries entirely increased in size (the left ovary more than the right), with a stretched, smooth surface of a white, mother-of-pearl colour, under which numerous cysts of a maximum diamater of 7-8 mm can be seen. The organ is hard to the cut and bleeds only slightly.

Histological Examination

A thin but evident band of collagen covers the ovarian cortex, poor in primordial and evolutive follicles, and rich, on the contrary, with microcystic formations and atresic follicles. The walls of the latter are made of theca cells placed in multiple layers with evident phenomena of vacuolization (so-called hyperthecosis with luteiniza-

[1] For abbreviations, see note 2, p. 86.

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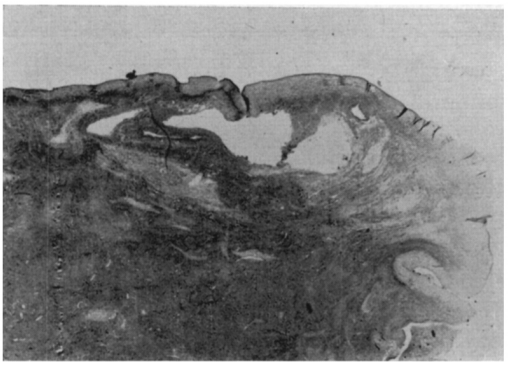

FIG. 3*a*

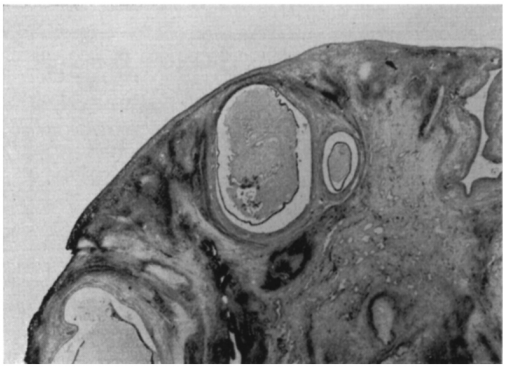

FIG. 3*b*

luteinized elements can only rarely be seen, appears to be less developed. The stroma is rich, more accentuated in the cortex and slacker and more oedemous in the medullar, which is full of numerous dilated blood vessels. Frequent findings of hyalin bodies of vascular origin. (Fig. 3*a*).

Last Report

Operated on the 8.VI.61, the patient began her menstrual cycles again after exactly one month; menstruation continued regularly with normal characteristics but preceded by menstrual syndromes.

The patient has since had four pregnancies. The first was followed by a premature birth at the 6th month; the foetus was born dead. The second was also interrupted at the 6th month with the death of the infant after 24 hours. The third and fourth pregnancies were completed with the birth of healthy living children.

After the operation, the patient noticed a considerable and spontaneous diminishing of hirsutism, but she has put on weight regularly (especially after the birth of her last child), also because she eats a lot of starchy foods.

tion). The stroma is rich and deep even at the level of the medulla, but often appears to be dissociated by phenomena of oedematic imbibition. The vascularization in some points outlines almost angiomatic aspects. (Fig. 3*b*).

Last Report

Operated on the 9.XI.65, the patient began menstrual cycles again after exactly one month; menstruation continued regularly afterwards. The patient went on a slimming diet with evident success at the beginning, but then she abandoned the diet and has now put on weight once more. The patient noted a certain spontaneous diminishing of hirsutism. At present she enjoys good health.

Family B.

Both parents are alive and healthy. The mother, menstrually normal, has only had the two pregnancies from which the two patients under our observation were born.

The father and a paternal aunt have quite evident hirsutism, but the aunt has no other abnormalities.

RENATA, AGED 19

Born at the 9th month with a forceps birth. First physiological functions normal.

Common exanthema. Tonsillectomy at the age of 6.

For several years, the patient has suffered from frontal headache, especially after work involving concentration.

Menarche at 10½. Amenorrhea for 6 months after the first cycle; the patient subsequently began spontaneous cycles which are, however, generally late, (even as late as 15 days). The length and quantity of the period is normal.

Slight premenstrual tension, especially mammary.

Since the age of about 15, the patient has had hirsutism; at first it was limited to the lower limbs; then it spread to the upper limbs and face.

Physical Observations

Short in stature, perfectly feminine somatic aspect.

Height 151 cm, weight 50.1 Kg.

Rosy skin; fair pigmentation.

Average hirsutism on the face, upper and lower limbs, umbilical line, sacral and navel regions.

EVA, AGED 16

Born at the 9th month by normal birth. First physiological functions normal.

Common exanthema. Tonsillectomy at the age of 12.

For some time the patient has suffered from headache, not precisely located. (The patient is very short-sighted.)

Menarche at 13½. Almost regular cycles for about a year, after which menorrhagia for 45 days. The patient was treated with progesterone and testosterone (3 injections); she had a period of amenorrhea for about 3 months; subsequently she began menstrual cycles again, but they are very irregular, and as late as 2 or 3 months. Lately the cycles have nearly always occurred after substitutive therapy.

Since menarche, the patient has had hirsutism, at first limited to the lower limbs but subsequently it spread to the whole body surface. (It does not seem that hirsutism increased after the injections of progesterone and testosterone.)

Physical Observations

Tall in stature, " ephebic " somatic aspect.

Height 159 cm, weight 45.5 Kg.

Dry skin; dark pigmentation.

Accentuated hirsutism on the face, limbs, breasts, umbilical line, sacral and navel regions.

Well developed breasts.

Normal external genitalia. (Triangular pubic hair region).

Common laboratory tests normal.

Pneumopelvigraphy: uterus within normal limits. Both ovaries are larger than normal, especially the right ovary which has a globular shape.

Moderately well-developed breasts.

Normal external genitalia. (Losange-shaped pubic hair region).

Common laboratory tests normal.

Pneumopelvigraphy: uterus within normal limits. Both ovaries are slightly larger than normal, especially the right ovary, which is globular in shape.

HORMONE TESTS [2]

Treatment	17-KS (mg)	DEA (mg)	17-OHCS (mg)	Phenolst. (μg)	FSH (R.U.)	17-KS (mg)	DEA (mg)	17-OHCS (mg)	Phenolst. (μg)	FSH (R.U.)
None	12.8	2.5	5.3	42.0	5	11.3	0.9	6.0	20.8	5
None	12.4	1.0	7.3	43.4		8.5	0.9	6.0	19.0	
Dexameth	7.1	0.9	2.8	27.3		6.7	0.5	4.4	12.9	
Dexameth	4.7	0.5	3.5	30.4		6.2	0.5	3.8	20.6	

Treated with contraceptive agents and dintoin for 4 months, subsequently the patient stopped the contraceptive agents, continuing with the dintoin.

The cycles reappeared normally even after suspending the treatment; there was evident regression of hirsutism.

Treated with contraceptive agents and dintoin for 4 months, subsequently the patient stopped the contraceptive agents, continuing with the dintoin.

The cycles reappeared normally even after suspending the treatment; there was evident regression of hirsutism, especially on the limbs and trunk, but less on the face.

DISCUSSION

The possibility that the Stein-Leventhal syndrome may be linked to genetic factors has been pointed at now for several years.

Some authors have in fact thought of the existence of *anomalies of a chromosomic order* (Jacobs et al. 1961) and others have put forward the hypothesis of a close relationship between the above-mentioned syndrome and gonadal dysgenesis in a wide

[2] Hormone techniques: 17-Ketosteroids (17-KS), Bigozzi et al. 1954; Deidroepiandrosterone (DEA), Jayle 1963; 17-Hydroxicorticosteroids (17-OHCS), Reddy et al. 1952; Phenolsteroids, Betes and Cohen 1947, modified; Gonadotropins (FSH), Albert 1964.

R. U. = rat units.

sense (Netter et al. 1961*a*, Serment et al. 1961, Williams et al. 1969, etc.). This possibility seems to be suggested, however, only by isolated clinical observations or by sporadic research of a karyologic type.

For some time now, some authors have pointed out the finding of a *negative nuclear chromatine* in women affected by the Stein-Leventhal syndrome (Vague et al. 1956, Belaisch et al. 1958, Wais 1960, Case Record 85 of the Massachusetts General Hospital 1962). Muller and Weill (1961), in quite a large study, revealed the presence of some cases of chromatine-positives, chromatine-negatives and of " intermediate, difficult to classify " ones. Moore (1962) in one case, found the Davidson test negative and the Barr test slightly positive.

In 1961 a group of French authors (Netter et al. 1961*a-b*, De Grouchy et al.) reported having observed chromosomal patterns of various types in three subjects affected by Stein-Leventhal syndrome (namely, XX/XXX, XX/XX, and XO/XY/-XX) and a karyotype XX_D in a case of transition between the Stein-Leventhal syndrome and gonadal dysgenesis.

Chromosomal anomalies have also been met with, later on, by other researchers. Leon et al. (1963) have observed a normal feminine karyotype in one case, and a pattern XX/XXY in another case; Bishun and Morton (1964) have noted a feminine karyotype in two cases, the pattern XX/XX_D in one, and a probable pattern XO/XX in another; and finally Hargrave (1965) has observed a pattern XO/XX in only one case.

On the other hand, other authors have steadily found a positive nuclear chromatine and a normal female karyotype (46,XX) in all the subjects observed: De Lozzio et al. (1963) in 2 cases; Byrd et al. (1964) in 9 cases; Van Campenhout et al. (1964) in 10 cases; Botellà-Llusià (1967) in 15 cases; Cooper et al. (1968) in 15 cases; and Jacobs et al. (1961), Bonilla (1962), Rashad et al. (1964), and Valsecchi et al. (1965) respectively in 1 case, etc.

Quite recently Stenchever et al. (1968) met with a normal karyotype in 40 out of 41 cases examined: only in one an autosomic anomaly (dimensions greater than normal in the short arm of a group-G chromosome in 29% of the cells examined) was present, but its importance in the genesis of ovarian abnormalities is quite doubtful. According to Netter and Thoret (1967), the " typical form of the Stein-Leventhal syndrome bears a normal karyotype ", as they were able to ascertain in " numerous cases ".

This observation stems from the data put together up to now, that the majority of subjects with ovarian abnormalities such as in the Stein-Leventhal syndrome, do not show anomalies at the chromosomal level, at least not anomalies detectable by the present techniques; and that the chromosomal aberrations met with in a few cases are too different to establish a relationship with the anatomical-clinical picture of the subjects affected.

One must remember that, within the vague limits of the syndrome, the criteria adopted by some authors for the diagnosis of the Stein-Leventhal ovary may in some cases be at least debatable; and in the gonadal dysgenesis with karyotype XO/XX

it is easy to meet with collagenism of the outer stroma of the dysgenetic gonad, and eventually with the presence of more or less large follicular cysts (Giusti et al. 1966).

A second possibility is that the disease may be linked to *genetic abnormalities*. In 1968, Cooper et al. dedicated an important contribution to this thesis.

Before 1968 indications of polycystic ovaries in two or more sisters, or in MZ twins already existed in the literature, but the authors generally failed to underline the interest of this observation.

In 1955 Rabinovich reported a patient with polycystic ovaries, oligomenorrhea, hirsutism, obesity, and hypertension; 6 sisters were obese and had hirsutism and menstrual abnormalities.

In 1956 Cerviño et al. accurately described two sisters affected by the Stein-Leventhal syndrome without making any comment on their family. Evans and Riley (1958) hinted at a pair of sisters with the disease when they came under observation, while Trace et al. (1960) reported two other sisters, but only in a summary-table of a larger case-list; from this table one can see that these sisters had an almost identical clinical, anatomical, and hormonal picture. In 1964 Van Ek described two sisters, aged 20 and 18 respectively, with secondary amenorrhea, but without other endocrine alterations (only the younger sister had moderate hirsutism on the lower limbs), in whom " typical " Stein-Leventhal ovaries were present.

Goldzieher and Green (1962) gave more importance to the observation of a "typical" Stein-Leventhal syndrome in a pair of MZ twins; and also Jeffcoate (1964), who had studied two other MZ twins aged 26 who, after both having had a child in the same month, at once showed signs of obesity setting in, hirsutism, oligomenorrhea, and sterility. The culdoscopy carried out in only one of the patients showed the existence of " typical " Stein-Leventhal ovaries. Finally, Lloyd et al. (1966) have briefly described two MZ twins aged 18 who underwent a wedge resection of the ovaries for clinical diagnosis and histology of the Stein-Leventhal syndrome, but who never had spontaneous menstruation after the operation.

Other rare cases also exist where the disease might have been present in both mother and daughter, but in reality only one of these (Case Record 43481 of the Massachusetts General Hospital, 1957) seems to be sufficiently documented.

Bret et al. (1955) have in fact described a woman aged 27 (1st case) with menarche at the age of 9½ with very heavy initial menstrual cycles. The patient also had bilateral polycystic ovaries with scanty hyperthecosis. The mother, who also had menarche at 9½ and a similar menstrual history, has had this one child after an "operation at the ovaries" which the patient cannot precisely describe. Case 43481 at the Massachusetts General Hospital (1957) concerns a young girl aged 13 with obesity, hirsutism, and secondary amenorrhea (after a single menstrual cycle.) The ovaries were very enlarged and presented the histological picture of Geist and Gaines's hyperthecosis. The mother, who also suffered from obesity and hirsutism, was operated for bilateral ovariectomy (obviously after the birth of the patient) in another hospital. The ovaries showed the same condition of diffused hyperthecosis.

Finally, Suzor and Falloux (1961) have observed a woman aged 35 with obesity, hirsutism, sterility, and amenorrhea, and with the Stein-Leventhal ovary bioptically ascertained. The patient had a daughter of 16, born before the beginning of the above-mentioned symptoms. She presented oligomenorrhea and the virilizing syndrome. According to the authors, she had exactly the same ovaric abnormalities as her mother, but the diagnosis was not ascertained " because of the tender age of the patient. "

Stein denied this possibility: in 1967 he in fact confirmed that, at least as far as the case histories collected by him were concerned, there was nothing to make one think that the disease is transmitted from mother to daughter. Many women operated by him had had daughters who were already married, and mothers of a family, and none of them had showed signs of " abnormalities which could make one think of the syndrome in question. "

In 1968, however, Cooper et al. published the results of the first systematic research on families of patients with the disease. Starting with 18 propositae, they found that in 5 families other cases of the Stein-Leventhal syndrome existed, ascertained by laparotomy or celioscopy; more precisely, they kept 3 sisters under observation in the genealogical group II, 2 sisters and 1 cousin in group XXVIII, and 2 sisters in group XXXI, 3 sisters in group XXXVIII, and 2 sisters in group XLVII.

The cases of this type seem, however, to be limited to a single generation: in fact, in none of the 14 mothers examined was the Stein-Leventhal syndrome diagnosed. The authors reveal that in only 5 of the mothers was oligomenorrhea present, with more or less elevated levels of urinary 17-KS. The slight hirsutism present in some cases was not considered as an important factor. Cooper et al. (1968), on the other hand, attribute great importance to the fact that the male relatives (fathers and brothers) of the women affected by the Stein-Leventhal syndrome were very hirsute, much more so than the male relatives of the women examined and found to be normal.[3] Finally, in several relatives (male and female) of the affected subjects, the authors claim to have met with a " slightly higher than normal adrenal activity ", based solely on the levels of urinary 17-KS and urinary 17-OHCS.[4]

Concluding, Cooper et al. (1968) state that:

1. " A hereditary basis to the Stein-Leventhal syndrome seems inequivocably demonstrated. "

2. The transmission of the disposition to the illness is indicative of a dominant inheritance.

3. The responsible gene is most probably located on an autosome rather than on the X-chromosome.

[3] Gonzalez-Gutierrez (1969) also stresses the frequency of hirsutism in the relatives, male and female, of the subjects affected by the Stein-Leventhal syndrome.

[4] It may be interesting to remember that, in 1960, Nicolosi had already met with a positive Patrono test (elevation of the urinary 17-KS after a progesterone load) in two apparently healthy female blood-relatives affected by the Stein-Leventhal syndrome, and with the test equally positive.

The research by Cooper et al. is undoubtedly interesting, and the possibility of the existence of genetic factors in the Stein-Leventhal syndrome must be carefully considered.

According to us, however, the above data do not seem to demonstrate so much a heredity of the syndrome in question as the frequent incidence of polycystic ovaries in families in which so-called simple hirsutism is present as a genetically transmitted characteristic. It is in fact well-known that the latter anomaly is sometimes hereditary and seems to be *transmitted as an incompletely dominant character not bound to sex* (Broster et al. 1953, Cahill and Melicow 1950, Touraine 1955, Milcu and Maximillian 1962, Milcu et al. 1968, etc.),[5] therefore just like what Cooper et al. have suggested for the Stein-Leventhal syndrome. Besides, in some families, the intensity of the manifestations tends to worsen from generation to generation (Cahill and Melicow 1950, Broster et al. 1953, Bigozzi et al. 1957), until more or less serious menstrual abnormalities appear in the females, which are very often associated with ovarian abnormalities of the polycystic type (Giusti et al. 1964).

It is well-known that the pathogenesis of simple hirsutism is still today the subject of much discussion. Some authors acknowledge the possibility that in some cases the abnormality is due to a " hypersensitivity of the target organs " at androgen levels, circulating perfectly normally (Lopez et al. 1967, etc.). Even so, since in several cases of simple hirsutism, also familial, the existence of more or less severe adrenal hyperandrogenism has been documented, one can put forward the hypothesis that the latter factor is responsible for the genesis of the ovarian polycystic abnormalities. Several authors in fact maintain that an excess of adrenal androgens can (even if not necessarily) produce ovarian changes of the polycystic type, indistinguishable on the morphologic plane from the true Stein-Leventhal syndrome, but different on the functional plane: amongst the forms in which this pathogenesis is recognizable, in fact, ovarian steroidogenesis would be normal (Kase et al. 1963, Mauvais-Jarvis and Baulieu 1962).

A similar interpretation could, for example, be valid for the B. sisters under our observation: simple hirsutism was in fact present in the paternal branch of the family, and both sisters showed relatively high values of urinary 17-KS, with moderate depression under dexamethasone.

On the other hand, since the Stein-Leventhal syndrome seems more often to be " fraternal " rather than transmitted from mother to daughter, one must also consider the possibility that in the mothers of the affected subjects conditions exist which are capable of influencing the fetal ovary in a negative sense; and these conditions may sometimes repeat themselves in subsequent pregnancies. Philipp and Stange (1954), for example, have attributed great importance to toxaemia in pregnancy in the pathogenesis of the Stein-Leventhal ovary.

Since the first pair of sisters we kept under observation (the R. sisters) were both

[5] Moncada-Lorenzo (1970) is favourable to a multifactorial heredity, but his arguments are not altogether convincing.

born after pregnancies threatened by serious phenomena of toxaemia, it seems only right to consider the possibility that, in this case, the " familial aspect " of the disease in these patients could be linked to the repetition of the same lesional factor in the course of embryonic development, rather than to genetic factors in a narrow sense.

To conclude, we maintain that sufficient elements exist supporting the existence, in certain cases, of predisposing genetic factors to the manifestation of the Stein-Leventhal syndrome, but that a true heredity of the disease cannot at the moment be entirely supported. Also certain " fraternal " cases could find an explanation in the lesional actions which are repeated during subsequent pregnancies. It is desirable, however, that research be continued in this direction, aiming to acquiring further information towards a better understanding and a more precise picture of the Stein-Leventhal syndrome, which is probably a *syndrome* in the strict sense of the word, that is, linked to pathogenetic moments which perhaps differ greatly from each other.

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RIASSUNTO

Gli autori descrivono due coppie di sorelle che presentavano alterazioni cliniche, morfologiche ed ormonali tali da poter essere inquadrate nell'ambito della « sindrome di Stein-Leventhal ».

Questi casi, insieme ad altre poche osservazioni consimili, suggeriscono la possibilità che la sindrome in questione sia condizionata, almeno in alcuni casi, da fattori di ordine genetico.

Dopo una breve rassegna della letteratura su questo particolare aspetto del problema, gli autori affermano che esistono elementi sufficienti per ammettere, almeno in certi casi, l'esistenza di fattori *predisponenti* alla comparsa della sindrome, ma che un'ereditarietà vera e propria dell'affezione non sembra per il momento sostenibile: tanto più che alcuni casi di sorelle affette potrebbero trovare spiegazione nell'azione di fattori lesivi ripetutisi nel corso di gravidanze successive.

RÉSUMÉ

Les auteurs décrivent deux couples de sœurs avec des altérations cliniques, morphologiques et hormonales typiques du « syndrome de Stein-Leventhal ».

Ces cas, ainsi que d'autres observations similaires, suggèrent la possibilité que ce syndrome soit, au moins dans certains cas, génétiquement conditionné.

Après une revue de la bibliographie sur ce sujet, les auteurs concluent que, tandis qu'il y a d'éléments suffisants pour admettre qu'au moins dans certains cas il existe une disposition génétique à ce syndrome, il n'est pas possible à ce moment d'affirmer que le syndrome soit héréditaire. Quelques observations de sœurs plus ou moins également atteintes pourraient s'expliquer par une action de facteurs lésifs, répétée au cours de différentes grossesses.

ZUSAMMENFASSUNG

Verf. beschreiben zwei Schwesternpaare mit klinischen, morphologischen und hormonellen Veränderungen, die in das Bild des « Stein-Leventhal-Syndroms » passen würden.

Diese Fälle sowie wenige andere Beobachtungen veranlassen die Frage, ob dieses Syndrom wenigstens in einigen Fällen nicht erbbedingt sei.

Nach einer kurzen Übersicht über das Schrifttum, das sich mit diesem Aspekt des Problems beschäftigt, glauben Verf., dass es genügend Elemente gibt, um wenigstens in einigen Fällen das Vorhandensein von prädisponierenden Faktoren für das Auftreten des Syndroms zuzugeben, dass man aber z.Zt. noch nicht behaupten kann, das Leiden sei erblich, umsomehr als sich einige Übereinstimmungen bei Schwestern durch die Wirkung von Verletzungsfaktoren erklären lassen, die sich im Laufe hintereinander folgender Schwangerschaften wiederholen.

Prof. A. Borghi, Via Andrea del Castagno 34, 50132 Firenze, Italy.