Gynecological Aspects of Female Familial Dysautonomia

Channa Maayan MD[1], Onit Sela MD[3], Felicia Axelrod MD[5], D'vorah Kidron MD[4] and Drorith Hochner-Celnikier MD[2]

Departments of [1]Pediatrics and [2]Gynecology, Hadassah University Hospital, Mt. Scopus and [3]Hebrew University – Hadassah Medical School, Jerusalem, and [4]Department of Pathology, Meir Hospital, Kfar Saba and Sackler Faculty of Medicine, Tel Aviv University, Israel; and [5]Familial Dysautonomia Center, New York University Hospital, New York, USA

Key words: familial dysautonomia, gynecology, premenstrual syndrome, pregnancy, birth, adenomyosis, dysgerminoma

Abstract

Background: Familial dysautonomia is a genetic disease in which there is a defect in the autonomic and sensory nervous systems. These systems have a major role in the reproductive system.

Objective: To study the inter-relationship of autonomic and sensory dysfunction and gynecological function.

Methods: The gynecological histories of 48 women with familial dysautonomia were analyzed retrospectively. Their mean age was 22.25 years (range 12–47). Thirty-three women (65%) were available for further questioning and investigation of hormonal status.

Results: Menarche had occurred in 32 of the 48 (66.7%). Their average age of menarche was significantly delayed as compared to their unaffected mothers (15.5 vs. 13.6 years respectively, $P=0.002$). The most prominent finding was the very high prevalence, 81.2%, of premenstrual symptoms. Seven of 26 had premenstrual syndrome symptoms of dysautonomic crisis. Blood sex hormone levels were normal in 27 of the 33 patients studied. None reached natural menopause. One patient had adenomyosis, and another, dysgerminoma. Three patients became pregnant and delivered healthy infants.

Conclusion: Menarche is delayed in women with FD, and the physiological monthly hormonal fluctuations may disturb autonomic homeostasis sufficiently to precipitate dysautonomic crisis.

IMAJ 2000;2:679–683

Familial dysautonomia is an inherited autosomal disease that affects the autonomic nervous system as well as the sensory and motor systems. The incidence of this disease among Ashkenazi Jews is 1:3703 [1]. The gene was mapped to chromosomal region 9q31 by linkage DNA markers [2].

The clinical signs and symptoms in FD patients involve most body systems [3]. Discoordination of the gastrointestinal tract causes feeding difficulties, choking, and gastroesophageal reflux. Autonomic crises are characterized by nausea, vomiting, hypertension, blotching, sweating, drooling and extreme nervousness, and are precipitated by any trigger that interferes with the body's homeostasis. The respiratory clinical manifestations are caused by aspiration of feeding or gastric content and lead to chronic lung disease. Restrictive lung disease appearing in these patients is attributed to kyphoscoliosis. The decreased CO_2 sensitivity and altered O_2 sensitivity in these patients causes unstable control of breathing. Dizziness and syncope are frequent manifestations and are secondary to unstable blood pressure. Neurological manifestations include altered skin sensitivity to pain and temperature, convulsions, ataxia, nystagmus, decreased muscle tone, and delayed developmental milestones. FD patients have no overflow tears and a decreased corneal sensation, hence their recurrent eye infections. Orthopedic problems include kyphoscoliosis and recurrent fractures.

The autonomic nervous system is essential for the normal function of multiple organ systems, including the reproductive system. Afferent neuronal fibers in the visceral organs participate in regulating hypothalamic hormonal output; efferent fibers play a role in the development of follicles; and fallopian tube motility may affect processes such as implantation, pregnancy and birth [4,5].

Neurotransmitters of the autonomic nervous system such as adrenaline, noradrenaline, and dopamine or acetylcholine are known to influence reproductive hormonal release [4,6] of gonadotropin-releasing hormone, prolactin, luteinizing hormone, follicle-stimulating hormone and melatonin [4,6]. Noradrenaline increases GnRH secretion while dopamine suppresses it. Dopamine and acetylcholine increase secretion of FSH. The ovaries are rich in sympathetic innervation and β receptors, especially in the perivascular areas surrounding follicles and secretory elements [7]. The autonomic innervation controls ovarian blood supply, secretions, follicular size, ovulation, contractility, and transport of ova through the aqueduct until implantation [4–6]. These β receptors are down-regulated by epinephrine and corticosteroids and up-regulated by LH and prolactin. Normal

FD = familial dysautonomia

GnRH = gonadotropin-releasing hormone
FSH = follicle-stimulating hormone
LH = luteinizing hormone

menstrual cycles are maintained by the pulsatile release of GnRH from the hypothalamus, which is affected by catacholamine. Noradrenaline levels during the pre-ovulatory phase are high and stimulate GnRH discharge. Dopamine has an inhibitory effect on GnRH, and with acetylcholine increases secretion of FSH. Prolactin, melatonin, and endogenous opiates are increased by stress hormones of the sympathetic nervous system [4,6,7]. Since the reproductive hormones are down-regulated by epinephrine and corticosteroids, interference with normal reproductive function might be expected in diseases such as FD in which the autonomic nervous system is dysfunctional.

Furthermore, with the increased life expectancy of these patients, more FD women will reach sexual maturity and ultimately menopause. Better understanding of their unique gynecological problems will help improve their quality of life and provide opportunities to evaluate the clinical manifestations of autonomic dysfunction on some gynecological functions.

Materials and Methods

The study population comprised 48 women who had been clinically followed at the Familial Dysautonomia Center at Hadassah University Hospital, Mt. Scopus for 16 years (January 1982 to January 1998). In each patient a positive histamine test showed the absence of flare following intradermal injection of histamine [3]. Genetic markers confirmed the diagnosis of FD [8].

The age of the patients ranged from 12 to 47 years (mean $22^{3/12}$±SD $9^{9/12}$ years, median age $19^{6/12}$ years). The mean age at diagnosis was 2.9±5.8 years. The clinical symptoms usually appear soon after birth. At the time of the study, of the 48 patients 13 were living (mean age $21^{10/12}$±$8^{10/12}$ years, median 20 years); 17 had died over the previous 15 years (mean $22^{9/12}$±$11^{5/12}$ years, median 16 years).The control group consisted of 22 unaffected mothers of the FD patients in the study.

Retrospective data were obtained from clinical questionnaires, patient interviews, and review of medical records. The data evaluated included age and weight at menarche, menstrual regularity, and hormonal profile (TSH, thyroxine, triiodothyronine, LH, FSH, d-hydroepiandosterone sulfate, androstendione, prolactin, testosterone, free testosterone, estradiol, progesterone and cortisol). Tests were performed only once in patients not yet achieving menarche. Others were evaluated at the 7th, 14th and 21st days of their menstrual cycles as follows: prolactin on the 7th day, all the above mentioned hormones on the 14th day, and prolactin and progesterone on the 21st day to evaluate ovulation. We also assessed premenstrual symptoms, pregnancy, childbirth and menopause. PMS was defined as the appearance of symptoms such as breast swelling and tenderness, a sensation of abdominal bloating, variable degrees of edema in the extremities, fatigue and depression, nausea, vomiting, headaches, acneform eruptions, and constipation occurring 3–7 days prior to each menstruation [9,10].

Statistical analyses were performed on data of menarche in FD patients and controls using the paired *t*-test and non-parametric test (Wilcoxon sign rank test). Correlation was performed on patients' age and weight at menarche.

Results

The following gynecological parameters were evaluated:

Age at menarche

Menarche was achieved in 32 of the 48 patients (66.7%); the remaining 16 (33.3%) had not yet achieved menarche (age range 12–16 years). The mean age of menarche was $15^{6/12}$±2.2 years, with an average delay of 23 months as compared to the patients' unaffected mothers [Figure 1], $P=0.002$ by paired *t*-test, $P=0.0015$ by Wilcoxon sign rank test. The patients' mean height and weight at menarche was 146.6±8.5 cm (range 123–160.3) and 36.4±5.250 kg (range 26.5–47.5), respectively. These measurements fall below the third percentile for the age-matched healthy population and are appropriate for the 50th percentile for the $11^{2/12}$ year-old population. While there was a negative correlation between patients' age at menarche and their weights, it did not reach statistical significance ($P=0.212$). The mean bone age measured in eight FD patients was $9^{3/12}$±3.6 years, while their chronological age was $13^{8/12}$±3.2 years.

Postmortem pathological examination of the ovaries of a 16-year-old FD patient with Tanner stage 0 showed numerous follicles in the inner cortex and primordial vesicular (antral) and graafian (mature) follicles. The outer cortex was composed of fibrotic ovarian stroma. No corpora lutea were found [Figure 2].

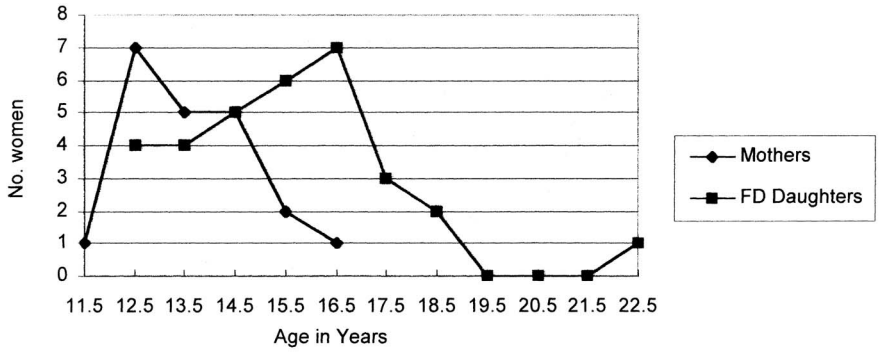

Figure 1. Age at menarche of FD women and their healthy mothers

PMS = premenstrual syndrome

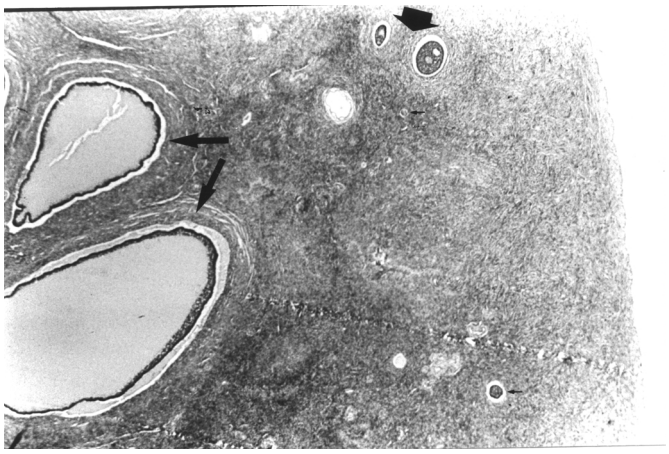

Figure 2. Ovarian cortex in a 16-year-old patient. Primordial (short arrows), pre-antral (thick arrow) and mature (long arrows) follicles are seen, with no evidence of corpus luteum (hematoxylin and eosin, x20).

Table 1. PMS symptoms in familial dysautonomia patients (do in two columns, not 4)

PMS symptoms (n=26)	
Abdominal pain	84.6%
Nausea	38.5%
Vomiting	30.7%
Depression	27%
FD crisis	27%
Nervousness	19.2%
Dizziness	19.2%
Headaches	15.4%
Acrocyanosis	11.5%
Fever	7.7%
Urine urgency	4.0%
Tremor	4.0%
Chest pain	4.0%

Menstruation regularity

Menstruation was regular in 21 of 32 patients (65.6%) and irregular in 11 (34.4%). Irregularity ranged from menses every 14 days to 6 months. Gynecological examination and pelvic sonogram were normal in all patients but one. In this patient gynecological examination revealed an enlarged uterus, and a pelvic sonogram demonstrated multiple fibroids.

Hormonal profile

Performed in 33 of the 48 FD patients, hormonal profiles were obtained for only 3 of the 17 deceased patients at the time of this study and in 30 of 31 living patients. All but seven patients showed a normal hormonal profile. Among the seven abnormal tests, five patients were found to have high prolactin levels ranging from 1,300 to 23,400 pmol/L (normal value for females ≤ 900 pmol/L); one patient had low LH (<0.6 u/L) and low FSH (1.38 u/L); and one patient had high DHEAS, 19.5 μmol/L (normal 2.2–11.7 μmol/L).

Premenstrual syndrome

Of 32 menstrual FD women, 26 (81.3%) suffered from PMS. The average duration was 4.25 days (range 1–14). Seven of these 26 had unique symptoms of PMS which are typical of FD crisis, namely nausea, vomiting, abdominal pains, hypertension, tachycardia, blotching, sweating and nervousness. The other FD patients had PMS with only one or two of these crisis symptoms [Table I]. All 26 patients suffering from PMS required medications. Eleven of 32 FD patients who were menstruating (34%) were on contraceptive pills (continuous combined oral contraceptive containing 20–35 μg ethyl estradiol): to alleviate PMS symptoms and/or menstrual irregularities. Among the 32 patients, 6 (18.7%) were taking analgesics such as paracetamol and ibuprofen, 7 (21.9%) were taking anti-anxiety drugs such as sulpiride, maprotiline, diazepam, or alprololam, and 2 (6.2%) were taking anti-emetic drugs such as metoclopramid or chlorpromazine. Eight of the 32 patients (25%) were taking a combination of the above medications. The sulpiride, maprotiline and metoclopramid most probably caused elevation of prolactin levels (see below).

Pregnancy and childbirth

Three FD patients achieved four pregnancies: one patient had an induced abortion and the two other patients delivered three healthy infants. During the pregnancies the women experienced episodes of unstable blood pressure caused by autonomic deficit. The pregnancies resulted in deliveries at 36–38 weeks gestation with birth weights ranging from 2.7 to 2.9 kg.

Menopause

Seven of 48 patients were over 35 years old and 3 were aged 45–47. No patients reached natural menopause. One patient underwent surgical menopause at age 47 because of severe dysmenorrhea and menometrorrhagia caused by uterus myomatus. She was treated with GnRH analogue for 7 months, but due to recurrence of symptoms hysterectomy and bilateral oophorectomy were performed. Histology revealed adenomyosis and multiple myomata.

Miscellaneous

One 27-year-old patient suffered menometrorrhagia for 2 weeks, associated with hypercalcemia of 14.6 mg/dl. After a huge abdominal mass was found, laparotomy revealed a 20 cm mass that was diagnosed as dysgerminoma stage 1A. To our knowledge this is the first case of an FD patient to be diagnosed with this tumor.

Discussion

Familial dysautonomia was first described by Riley and Day in 1949 [11], and until 20 years ago FD was considered a pediatric disease. However, increased knowledge and better treatment of FD patients have brought about a significant

DHEAS = d-hydroepiandosterone sulfate

increase in their life expectancy [12], such that today female FD patients have to cope with clinical problems like sexual maturation, menstruation, pregnancy, birth, and even menopause. The present study evaluated these parameters in 48 FD women ranging in age from 12 to 47 years.

We found that in FD patients the mean age at menarche was delayed and their weight significantly lower than in the general population. In a 16-year-old patient, the absence of corpus lutea in the ovary was consistent with delay of menarche [Figure 2]. The patients' mean weight at menarche was 11.6 kg lower than the average weight at normal menarche, 48 kg [13]. Since FD is a chronic disease affecting all body systems, the mean height and weight percentiles of FD patients are usually lower than normal. These differences stem from the effect of the high metabolic demand of a chronic disease, as well as recurrent lung infections, nausea and vomiting crises, poor to moderate nutritional intake, and a tendency toward low fat consumption. Women with moderate weight loss (10–15% of ideal weight) as well as the severe weight loss seen in anorexia nervosa (30% of their ideal weight) often experience primary or secondary amenorrhea [14]. It has been shown that a body fat ratio of 26–28% in mature women is necessary for maintaining regular ovulatory cycles [14].

Delayed sexual maturation is associated also with other chronic diseases, such as juvenile rheumatoid arthritis [15], β thalassemia major [16], sickle cell anemia [17] and celiac disease [18]. In our study the delayed bone age in the FD patients, as well as their reduced body fat, support the hypothesis that the delay in menarche is most probably not attributable to a direct effect of the autonomic nervous system on the ovaries but rather to the chronic disease state.

Most of the FD patients in the study group had regular menses (66%), and 11 of them (34%) had mildly irregular cycles. Five FD patients had hyperprolactinemia, which is known to play an important role in menstrual regularity. In two patients hyperprolactinemia was secondary to drugs such as sulpirid, maprotiline and metoclopramide. In the other three patients, repeated prolactin levels were normal, and the hyperprolactinemia was most probably related to stress [3]. In the other eight FD patients with irregular menses no hormonal abnormality was found, which may have been the result of stress, depression, chronic illness or some unknown cause.

The fact that most of the plasma sex hormone levels were normal is an important observation, possibly indicating that the defect of the autonomic nervous system in these patients does not affect sex hormone production and secretion.

The most prominent finding in the present study was that most of the FD patients studied suffered from PMS (81.25%), and in 27% it presented as FD crisis. The pathogenesis of FD crisis is not yet fully understood, but it is a unique and specific phenomenon of this disease. It appears in both male and female FD patients and is usually triggered by any disturbance of body homeostasis, e.g., stress, emotional events, disease, or gastroesophageal reflux. In female FD patients, hormonal changes during the menstrual cycle might trigger their appearance. As is the case with PMS in the general population, it occurs 2–3 days prior to menstruation and lasts for 2–4 days, usually into the menstrual period. The symptoms recur with each menses and include symptoms of FD crisis, namely constant nausea and vomiting, high blood pressure, sweating, drooling, blotching, nervousness, agitation and abdominal pains [3]. In our study the crisis was severe enough to require hospitalization in several cases. In all patients PMS interfered with their normal lifestyle sufficiently to warrant intervention such as treatment with oral contraceptives, which relieved symptoms and often prevented FD crisis. Any of the above symptoms of FD crisis could also appear as an isolated symptom of PMS, without a full crisis [Table 1]. Other medications used to treat these various symptoms included analgesics, triclofos sodium, chloropromazine and metoclopramide. Dizziness, acrocyanosis and tremor, which could be explained by a fall in blood pressure, were also noted in PMS. Blood pressure in FD is unstable, and may fall even more as a result of heavy bleeding, anemia, and depletion of body fluids because of reduced drinking and/or increased sweating or vomiting. An increase in body temperature (up to 38°C) was also observed as part of PMS in FD. In acute intermittent porphyria there is also exacerbation of the disease symptoms associated with menstrual periods. The occurrence of these attacks has been suppressed with hormonal therapy [19]. PMS in the general population usually appears later in life (30–40 years), but in FD patients PMS was usually evident as soon as regular menses were established. This may indicate that PMS in FD patients stems from a different mechanism.

FD women married to FD carriers may give birth to FD children. Among Ashkenazi Jews 3% are FD carriers [1]. An FD carrier test is currently performed in non-FD couples by genetic haplotype markers [8,20], and prenatal diagnosis is indicated only when the spouse is an FD carrier [21].

Pregnancies in FD women are considered high risk, particularly because of abrupt changes in blood pressure [22]. High blood pressure secondary to FD may be difficult to differentiate from toxemia or other causes of increased blood pressure in pregnancy. In FD there is no compensatory tachycardia with low blood pressure, therefore greater awareness of volume loss and low blood pressure is indicated.

While FD is associated with a deficiency in the peripheral sensory system of pain and temperature [23], there is normal visceral pain sensation. Thus the pain of abdominal contractions at birth and thereafter are felt normally, and analgesia should be provided accordingly. Surgery for kyphoscoliosis (spine fusion) or distorted small pelvic bones may justify elective cesarean section. If possible, general and spinal block anesthesia should be avoided because of unstable blood pressure, and epidural anesthesia is pref-

erable [24]. However, if general anesthesia is indicated, special measures for FD anesthesia should be taken into consideration because of unstable blood pressure, relative insensitivity to PCO_2 and altered PO_2 sensitivity [3], and hypersensitivity to sympathetic and parasympathetic drugs [25].

Postoperative complications in FD women include aspiration, atelectasis and deterioration of chronic lung disease subsequent to difficulty in coughing. The stress of vaginal or cesarean birth can trigger an FD crisis.

None of our FD patients reached natural menopause. One patient underwent bilateral oophorectomy that resulted in surgical menopause. Theoretically, vasomotor symptoms and exaggeration of normal climacteric symptoms could be expected, including FD crisis. It is expected that in the future more patients will reach menopause, and only then can clinical conclusions be drawn.

Conclusions

Female FD patients have special gynecological problems and needs. Menarche is delayed, but once established most patients experience regular menses. However, hyperprolactinemia secondary to anti-anxiety or anti-emetic drug therapy can cause irregular menses. The most unique feature of FD patients who achieve menarche is severe PMS symptoms manifested as FD crisis. An efficacious means of relieving and preventing PMS symptoms is the use of oral contraceptives. Prior to pregnancy, husbands of FD women should undergo genetic testing to determine if they are FD carriers. Pregnancy and birth in FD patients require special care.

As the life expectancy of FD patients increases, we must expect more women to reach sexual maturity and ultimately menopause. Better understanding of the unique gynecological problems of this population will help improve their quality of life.

Acknowledgement: Part of this work was carried out by O. Sela as a requirement for the M.D. qualification of the Hebrew University-Hadassah Medical School, Jerusalem, Israel.

References

1. Maayan C, Kaplan E, Shachar S, Peleg O, Godfrey S. Incidence of familial dysautonomia in Israel 1977–1981. *Clin Gen* 1987;32:106–8.
2. Blumenfeld A, Slaugenhaupt SA, Axelrod FB, Lucente DE, Maayan C, Libert CB, Ozelius L, Trofatter JA, Maines JL, Breakefield XD, Gusella JF. Localization of the gene for familial dysautonomia on chromosome 9 and definition of DNA markers for genetic diagnosis. *Nat Genet* 1993;4:160–4.
3. Axelrod FB, Maayan C. Familial dysautonomia. In: Chernick V, Boat F, eds. Kendig's Disorders of the Respiratory Tract in Children. Philadelphia: WB Saunders, 1998:1103–6.
4. Shenker JG, Meirow D, Schenker E. Stress and human reproduction. *Eur J Obstet Gynaecol Reprod Biol* 1992;45:1–8.
5. Lara HE, McDonald JK, Ojeda SR. Involvement of nerve growth factor in female sexual development. *Endocrinology* 1990;126:364–75.
6. Dodd J, Role LW. The autonomic nervous system. In Kandel ER, Swartz JH, Jessel TM, eds. Principles of Neural Science. Third edition. Norwalk, CN: Appleton and Lange, 1991:761–75.
7. Stjerquist M. Innervation of ovarian and testicular endocrine cells. In: Unsicker K, ed. Autonomic Endocrine Interactions. (Burnstock G, series ed). The Autonomic Nervous System. Harwood Academic Publishers, 1996:231–56.
8. Blumenfeld A, Slaugenhaupt S, Liebert CB, Temper V, Maayan C, Gill S, Lucente DE, Idelson M, MacCormack K, Monahan MA, et al. Precise genetic mapping and haplotype analysis of the familial dysautonomia gene on human chromosome 9q31. *Am J Hum Genet* 1999;Suppl.64:1110–18.
9. Reid RL, Yen SSC. Premenstrual syndrome. *Am J Obstet Gynecol* 1981;139(1):85–104.
10. Bancroft J. The premenstrual syndrome – a reappraisal of the concept and evidence. [Synopsis]. *Psych Med* 1993;Supple.24:1–47.
11. Riley CM, Day RL, Greeley D, Langford WS. Central autonomic dysfunction with defective lacrimation. *Pediatrics* 1949;3:468–78.
12. Axelrod FB, Abularrage JJ. Familial dysautonomia: a prospective study of survival. *J Pediatr* 1982;101:234–6.
13. Goldsmith LT, Weiss G. Puberty, menarche and clinical aspects of normal menstruation. In: Scott JR, Di Saia PhJ, Hammond CB, Spellacy WN, eds. Danforth's Obstetrics and Gynecology. Sixth ed. Philadelphia: JB Lippincott, 1990:739–41.
14. Frisch RE. The right weight: body fat, menarche, and ovulation. *Baillieres Clin Obstet Gynecol* 1990;4:419–39.
15. Fraser PA, Hoch S, Erlandson D, Partridge R, Jackson JM. The timing of menarche in juvenile rheumatoid arthritis. *J Adolesc Health Care* 1988;9:483–7.
16. Saka N, Sukur M, Bundak R, Anak S, Neyzi O, Gedikoglu S. Growth and puberty in thalassemia major. *J Pediatr Endocrinol Metab* 1995;8:181–6.
17. Singhal A, Thomas P, Cook R, Wierenga K, Serjeant G. Delayed adolescent growth in homozygous sickle cell disease. *Arch Dis Child* 1994;71:404–8.
18. Chavez E, Ceresa S, Gnevara G, Espinoza J, Pizarro B, Rossel M. Celiac disease in adolescents. *Rev Chier Pediatr* 1991; 62:238–41.
19. Lamon JM, Frykholm BC, Herrera W, Tchudy DP. Danazol administration to females with menses: associated exacerbation of acute intermittent porphyria. *J Clin Endocrinol Metab* 1979;48:123.
20. Oddoux C, Riech E, Axelrod FB, Blumenfeld A, Maayan C, Slaugenhaupt S, Gusella I, Ostrer H. Prenatal diagnostic testing for familial dysautonomia using linked genetic markers. *Prenat Diagn* 1995;817–26.
21. Eng CM, Slaugenhaupt SA, Axelrod FB, Gusella JF, Desnick RJ. Prenatal diagnosis of familial dysautonomia by analysis of linked CA-repeat polymorphisms on chromosome 9 q31-q33. *Am J Med Genet* 1995;59:349–55.
22. Porges RF, Axelrod FB, Richards M. Pregnancy in familial dysautonomia. *Am J Obstet Gynecol* 1978;132:485–8.
23. Axelrod FB, Iyer K, Fish I, Pearson J, Sein ME, Spielholz N. Progressive sensory loss of familial dysautonomia. *Pediatrics* 1981; 67:517–22.
24. Leiberman JR, Cohen A, Wiznitzer A, Maayan C, Greenberg L. Cesarean section by local anesthesia in patients with FD. *Am J Obstet Gynecol* 1991;165:110–11.
25. Axelrod FB, Donenfeld RF, Danziger F, Turndorft H. Anesthesia in familial dysautonomia. *Anesthesiology* 1988;68:631–5.

Correspondence: Dr. C. Maayan, Dept. of Pediatrics, Hadassah Hospital, Mt. Scopus, P.O. Box 24035, Jerusalem 91240, Israel. Tel: (972-2) 584-4510; Fax: (972-2) 582-3515
email: cmaayan@hadassah.org.il

A little rebellion now and then is a good thing.

Thomas Jefferson, third President of America (1743–1826)