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ACCIDENTAL GYNECOMASTIA IN CHILDREN

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ABSTRACT

Any palpable breast tissue in men is abnormal except during: the neonatal period, adolescence and in elderly age. Gynecomastia in prepubertal children may be due to enhanced endogenous oestrogen production, drugs or unknown causes. After the onset of puberty gynecomastia may also be due to a deficiency of testosterone. Young men and boys are particularly sensitive to oestrogens and may develop gynecomastia from exposure to industrial oestrogen, to creams containing oestrogens, to antiandrogens or to unrecognized endocrine substances. Furthermore gynecomastia and others pubertal disorders in males and females may be due to ingestion of food containing oestrogens or oestrogen-like substances; many "epidemics" of gynecomastia among children have been described. Hormones ingested by meat can cause breast enlagement and other deleterious immediate or long term effects. In particular it is a common concern among paediatricians and endocrine specialists that environmental and dietary "contaminants" may interfere with the pubertal development. In the evaluation of all this data we can not ignore the toxic effects of contamination may be having both in the short term but, more particularly, in the long term in terms of morbidity, mortality and therefore social costs.

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Introduction

Any palpable breast tissue in men is abnormal except for three situations:

1. The transient gynecomastia of the newborn; this condition is present in many newborns and it is probably due to maternal and/or placental oestrogens (1).
2. The breast enlargement at puberty in boys: this phenomenon is a frequent (30-75%) occurrence in male adolescence; the exact cause is uncertain. It is presumably due to the fact that in boys, during the early stage of puberty, the plasma ratios of testosterone to estradiol and of adrenal androgens to estrone tend to be low. Gynecomastia usually resolves in 2-3 years. Pubertal gynecomastia starts on average between the age of 10 and 12 years with a peak occurrence between ages 13 and 14 (2-5).
3. Gynecomastia that occasionally occurs in elderly men (6).

A confounding problem in the ascertain of gynecomastia and premature thelarche is that it may be difficult to distinguish true enlargement of breast tissue from lipomastia, in which the enlargement is due to adipose tissue. This condition is very common in overweight children. True glandular breast tissue can be defined from lipomastia by ultrasonography and generally mammography is not required in defining breast tissue.

Causes of gynecomastia

Gynecomastia may be due to:

1. Endocrine disorders:
   - Deficiency of testosterone: when gynecomastia occurs as a consequence of failure of testosterone synthesis (or action), it is generally associated with elevations of plasma gonadotropin levels and may or may not be associated with a secondary rise in oestrogen secretion.
   - Increased oestrogen production: this alteration can result from increased testicular oestrogen secretion, from increased substrate for extraglandular formation, or from increased extraglandular aromatase itself.
2. Drugs, foods and environmental factors by several different mechanisms.
3. Unknown causes.

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Gynecomastia and drugs

Drugs can cause gynecomastia by several mechanisms. Oestrogens administrated to males can result in severe gynecomastia. Young men and boys are particularly sensitive to oestrogen and may develop gynecomastia from industrial oestrogen exposure or from exposure to dermal ointments containing oestrogens, which are sometimes used without being aware that the creams contain oestrogens.

Gynecomastia has been described in children exposed to oestrogenic cream used by the child's mother (7). Gynecomastia may also develop as the result of subtle environmental exposure to oestrogens, to antiandrogens, or to unrecognised endocrine substances. In particular gynecomastia has been described in children of workers in a DES manufacturing plant, due to absorbtion of DES from the fathers' clothing (8).

Gynecomastia has been observed in adolescents using anabolic steroids to enhance athletic performance. Anabolic steroids decrease testosterone production, decrease spermatogenesis and induce testicular atrophy; in this case gynecomastia results from an imbalance in the testosterone to estradiol ratio. Anabolic steroids may also induce other rare and severe side effects such as malignancies and thrombotic phenomena (9).

Phyto-oestrogens present in marijuana can cause breast enlargement by stimulation of the oestrogen receptors. Amphetamine abuse has also been associated with gynecomastia although its mechanism is still unclear. Thus any adolescent male presenting gynecomastia should be questioned about the use of illicit drugs (4).

Gynecomastia is also described as possible side effect of growth hormone (GH) therapy both in paediatric and in elderly patients as GH has specific receptors in the mammary tissue stimulating glandular proliferation (10-12). For this reason any patient treated with growth hormone should be monitored for breast disorders.

Gynecomastia and food

Gynecomastia and other pubertal disorders in males and females may be also due to ingestion of food containing oestrogens or oestrogen-like substances. Such agents may be derived from meat and dairy products from animals treated with oestrogenic implants or from fungal oestrogens and phyto-oestrogens in foods (6).

Although the toxic effects of steroids in animals and man have been well documented, such substances are still largely used in numerous countries for growth promotion, as the laws are highly variable from country to country.

The use of such substances for growth promotion has been banned in Italy since the '80s after an EC directive, which is also valid for other EU countries. In contrast, controlled use of such growth promoters is allowed in the USA, Canada and Latin America.

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Even in countries in which use is banned, these substances are frequently used illegally, and more and more cases are being uncovered. Hormonal growth promoters allow a 20% increase in weight in treated animals, and therefore give a significant economical benefit. The use of such hormones as growth promoters is most advantageous in the veal and poultry markets (13).

The effects of hormone ingestion through food may cause two types of toxic effects: immediate and long term.

Immediate effects depend on the age and sex of the subject, and include precocious thelarche, precocious pubarche, precocious puberty, gynecomastia, abnormalities of the menstrual cycle, decreased sperm count, sterility, decreased sexual desire and fetal malformations. (2, 14-19).

The main long-term effect, which is dependent on age and sex, but mainly on the dose and exposure time, is the carcinogenicity of these growth promoters.

In the literature there are many evidences that oestrogens and androgens influence breast cancer risk. (20-22).

In particular diethylstilbestrol (DES) has been shown to be carcinogenic both in animals and in man. Herbst's observation in the 70's of the high incidence of vaginal adenocarcinoma in adolescents born of mothers treated with DES during pregnancy is known worldwide (23).

This observation was confirmed in the following years with studies proving the toxicity of DES (14, 24, 25).

In the 80's there was a case of a young man exposed to DES in utero who developed malformations of the reproductive system and seminoma in later years (26).

More recent studies have confirmed the toxic effects of DES on the male reproductive system (19). Despite such evidence there was a high concentration of DES in baby foods in Italy up to the '80s. This was revealed during quality controls and showed the inefficiency or absence of sufficiently rigorous food controls (27). Even though the use of DES in livestock rearing is strictly banned worldwide, this substance is still illegally used as growth promoter, as Swiss police recently revealed.

Toxic effects related to growth promoters and their ingestion through contaminated meat has also been described in children. Most interesting are the reported cases of abnormal pubertal development such as precocious thelarche, gynecomastia, and precocious puberty, which occasionally resemble epidemics.

In 1979 in Italy we described an epidemic of gynecomastia and thelarche in a large pediatric population. 213 boys aged 3-14 yrs and 110 girls aged 3-7 yrs were studied. Breast enlargement was present in 29% of boys and in 21% of girls aged 3-5 yrs, in 58% of boys aged 6-10 yrs and in 67% of girls aged 6-7 yrs. Breast enlargement disappeared within 8 months and although oestrogenic contamination was not proven an accidental contamination of the meat was suspected as the cause of the outbreak. (2).

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In the '80s in Italy isolated cases of pseudo-precocious puberty linked to contaminated meat ingestion were recorded (28).

In Puerto Rico anomalous sexual development was a major public health problem in the '80s. In those years a total of over 10.000 cases of anomalous sexual development were documented by Perez Comas and by the Puertorican Department of Health Thelarche Survey, which were established as a consequence of the increasing health problem. The manifestations were variables: gynecomastia, premature thelarche, precocious puberty, polycystic ovaries. In particular Puerto Rico was found to have the highest incidence of pubertal disorders worldwide. In this outbreak the authors described an association with the consumption of poultry contaminated with oestrogens, as well as with environmental contamination caused by pharmaceutical industries producing estroprogestinics. Total serum oestrogens were high in more than 80% of subjects tested (males and females) (15, 17, 18).

Conclusions

It is a common concern among paediatricians and endocrine specialists that environmental and dietary "contaminants" may interfere with the pubertal development (29). In the 90's more and more cases of advanced pubertal development are being registered especially in the female population. It is also a common finding among paediatricians that there is an increasing number of female patients in whom pubertal progression is noticed before the age of nine years, thus creating a tendential decrease in the age at menarche (30).

Numerous authors around the world have noticed this decrease in age at menarche and it has been attributed to both genetic and environmental factors (31-34). Possible causes include environmental contamination, food contamination, increased prevalence of obesity and altered socioeconomic status.

In the USA it has been demonstrated that in females a tendency of advanced pubertal development is linked with increasing prevalence of obesity (35). In males an increase in weight has a variable effect on pubertal development (36). An increase in fat mass with the subsequent increase in leptin secretion could be one of the factors causing hypothalamic activation and the early onset of pubertal changes (37, 38).

One American study carried out on a very large sample population showed that about 60% black girls and 30% Caucasian girls show signs of puberty before the age of 9 years (39).

In the evaluation of all this data we can not ignore the toxic effects that environmental and dietary contamination may have both in the short term but, particularly, in the long term for morbidity, mortality and therefore social costs.

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References

1. McKiernan JF, Hull D. Breast development in the newborn. Arch Dis Child 1981;56:525-9.
2. Fara GM, Del Corvo G, Bernuzzi S, Bigatello A, Di Pietro C, Scaglioni S, et al. Epidemic of breast enlargement in an Italian school. Lancet 1979; 2:295-7.
3. Sizonenko PC. (eds) Pediatric Endocrinology. Williams and Wilkins, Baltimore 1993:387.
4. Braunstein GD (eds) Pediatric Endocrinology. Fima Lifshitz, New York 1996:197.
5. Sopena M, Salvador J. Gynecomastia. Revista de Medicina de la Universidad de Navarra 1997; 41:42-50.
6. Frantz AG, Wilson JD. (eds) Williams Textbook of Endocrinology. Saunders Company, Philadelphia 1992:961.
7. Felner E, White PC. Prepubertal gynecomastia: indirect exposure to estrogen cream. Pediatrics 2000;105:853.
8. Pacynski A, Budzynska A, Przylecki S, Robaczynski J. Hyperestrogenism in pharmaceutical factory workers and their children as an occupational disease. Endokrynologia Polska 1971; 22:149-54.
9. American Academy of Pediatrics-Committee on Sports Medicine and Fitness, (no authors given). Adolescents and anabolic steroids: a subject review. Pediatrics 1997;6:904-8.
10. Allen DB. Safety of human growth hormone therapy: current topics. J Pediatr 1996;128:S8-13.
11. Mertani HC, Garcia-Caballero T, Lambert A, Gerard F, Palajer C, Boutin JM, et al. Cellular expression of growth hormone and prolactin receptors in human breast disorders. Int J Cancer 1988;79:202-11.
12. Sullivan DH, Carter WJ, Warr WR, Williams LH. Side effects resulting from the use of growth hormone and insulin-like growth factor-I as combined therapy to frail elderly patients. J Gerontol A-Biol 1998;53:M183-7.
13. Gatti GL, Macri A, Ortolani E. (eds) (1982) Studi farmaco-tossicologici sui rischi connessi con 1'impiego di sostanze ormonali come auxinici in zootecnica. Bollettino Istituto Superiore di Sanita Italia., Ed. ISS, Roma, 10.
14. Bibbo M, Gill WB, Azizi F, Blough R, Fang VS, Rosenfiel RL, et al. Follow-up study of male and female offspring of DES-exposed mothers. Obstet Gynecol 1977;49:1-8.
15. Perez Comas A. Precocious sexual development: clinical study in the western region of Puerto Rico. Boletin-Asociacion Medica de Puerto Rico 1982;74:245-51.
16. Saenz CA, Toro-Sola M, Conde L, Bayonet-Rivera NP. Premature thelarche and ovarian cyst probably secondary to estrogen contamination. Boletin-Asociacion Medica de Puerto Rico 1982; 74:16-9.
17. Freni-Titulaer LW, Cordero JF, Haddock L, Lebron G, Martinez R, Mills JL. Premature thelarche in Puerto Rico. A search for environmental factors. AJDC 1986;140:1263-7.
18. Perez Comas A. Premature sexual development in Puerto Rico. Boletin-Asociacion Medica de Puerto Rico 1988;80:85-90.

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19. McLachlan JA, Newbold RR, Li S, Negishi M. Are estrogens carcinogenic during development of the testes?. APMIS 1998;106:240-4.

20. Barrett JS, Tsutsui T. Mechanisms of estrogen-associated carcinogenesis. Prog Clin Biol Res 1996;394,105-11.

21. Key TJ. Serum oestradiol and breast cancer risk. Endocr.-Relat. Cancer 1999;6:175-80.

22. Yu H, Diamandis E, Hoffman B. Elevated estradiol and testosterone levels and risk for breast cancer. Ann Intern Med 1999;131:715-716.

23. Herbst AL, Scully RE. Adenocarcinoma of the vagina in adolescence. A report of 7 cases including 6 clear-cell carcinomas (so-called mesonephromas). Cancer 1970;25:745-57.

24. Herbst AL, Robboy SJ, Scully RE. Poskanzer DC Clear-cell adenocarcinoma of the vagina and cervix in girls: analysis of 170 registry cases. Am J Obstet Gynecol 1974;119:713-24.

25. Lamb JC, Newbold RR, McLachlan JA. Evaluation of the transplacental toxicity of diethylstilbestrol with the scanning electron microscope. J Toxicol Env Health 1979;5:599-603.

26. Conley GR, Sant GR, Ucci AA, Mitcheson HD Seminoma and epididymal cysts in a young man with known diethylstilbestrol exposure in utero. JAMA 1983;249:1325-6.

27. Loizzo A, Gatti GL, Macri A, Moretti G, Ortolani E, Palazzesi S. Italian baby food containing diethylstilboestrol: three years later. Lancet 1984;1:1014-5.

28. Pasquino AM, Balducci R, Manca Bitti ML, Spadoni GL, Boscherini B. Transient pseudo-precocious puberty by probable oestrogen intake in 3 girls. Arch Dis Child 1982;57:954-6.

29. Andersson AM, Skakkebaek NE. Exposure to exogenous estrogens in food: possible impact on human development and health. Eur J Endocrinol 1999;140:477-85.

30. Herman-Giddens ME, Slora EJ, Wasserman RC, Bourdony CJ, Bhapkar MV, Koch GG, et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Setting network. Pediatrics 1997;99:505-12.

31. Chie WC, Liu YH, Chi J, Wu V, Chen A. Predictive factors for early menarche in Taiwan. J Formes Med Assoc 1997;96:446-450.

32. Sanchez-Andres A. Genetic and environmental factors affecting menarcheal age in Spanish women. Anthropologischer Anzeiger 1997;55:69-78.

33. Muscari ME, Faherty J, Catalino C. Little women: early menarche in rural girls. Pediatric Nursing 1998;24:11-5.

34. Milenkovic S, Milenkovic M. Age at menarche in Eastern Serbia. Horm Res 2000;53:93.

35. Wattigney WA, Srinivasan SR, Chen W, Greenlund KJ, Berenson JS. Secular trend of earlier onset of menarche with increasing obesity in black and white girls: the Bogalusa Heart Study. Ethnicity & Disease 1999;9:181-9.

36. Slyper AH. Childhood obesity, adipose tissue distribution, and the pediatric practitioner. Pediatrics 1998;102:131-2.

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37. Mantzoros CS, Flier JS, Rogol AD. A longitudinal assessment of hormonal and physical alterations during normal puberty in boys. Rising leptin levels may signal the onset of puberty. J Clin Endocr Metab 1997;82:1066-70.

38. Licinio J, Negrao AB, Mantzoros C, Kaklamani V, Wong ML, Bongiorno PB, et al. Synchronicity of frequently sampled, 24-h concentrations of circulating leptin, luteinizing hormone, and estradiol in healthy women. Proceedings of the National Academy of Sciences of the United States of America 1998;95:2541-6.

39. Morrison JA, Barton B, Biro FM, Sprecker DL, Falkner F, Obarzanek E. Sexual maturation and obesity in 9- and 10-year-old black and white girls: the National Heart, Lung and Blood Institute Growth and Health Study. J Pediatr 1994; 124:889-95.

Discussion

Mike Joffe (London, UK) How did you measure fertility in your follow-up study?

Giuseppe Chiumello (Milan, Italy) As parameters of fertility, we considered the regularity of menses, the occurrence of pregnancies and miscarriage, the number of conceived children and the recourse to a fertility-care unit. We also considered as a parameter of infertility a period larger than 12 months of unprotected sexual intercourse without conceiving.

Patrick Thonneau (Toulouse, France) How did you choose your controls, and can you be sure that the controls had not eaten the same food thereby being exposed to the same diet with oestrogen or diethylstilboestrol (DES)? What was your period of follow up?

Giuseppe Chiumello We tried to ensure that our controls were as similar as possible to the exposed subjects. The case group came from a private school in the pre-metropolitan area from medium to high socio-economic levels families. Controls were recruited in private schools of Milan using the register of 1977. The cases: Controls ratio was about 1:3. Controls were between 3 and 13 years of age at that time (1977), and the social status, the age and sex distributions, and the geographical areas were similar between the cases and controls. We are not sure that they had not been exposed to a subtle contamination. Moreover, we know that they did not have accidental gynaecomastia (or other pubertal disorders) with a significant prevalence at that time.

Anna-Maria Andersson (Copenhagen, Denmark) Was the breast enlargement in your children due to a single accident causing high level exposure or was there exposure over a longer time interval? It is important to know if a single episode of accidental exposure can have any effect.

Giuseppe Chiumello Both possibilities were considered but we cannot achieve any conclusion.

Peterson Myers (Virginia, USA) Both bisphenol A and nonylphenol are commonly used as surfactants in insecticide mixtures, and are labelled as inert ingredients. Many schools even nowadays have fairly aggressive pest control programmes, and I suspect that in 1979 this was even more common. Did you consider such compounds as the source of oestrogen in your study?

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Giuseppe Chiumello We checked this possibility in the school, but we were unable to demonstrate it and we cannot exclude the possibility. We could not trace the meat because it had already been consumed and the Police Department was unable to investigate a sample from the provider of meat to the school. We assumed that the meat was the source of the contamination because everything else was checked. Subsequent samples of meat from that provider were free from oestrogens when tested by the Police Department.

Jorma Toppari (Turku, Finland) Small testicular size of less than 12 ml is expected to be associated with decreased inhibin B and increased FSH levels. Do you have any hormone level data from your study of gynaecomastia in the Italian school?

Giuseppe Chiumello There was no significant differences in inhibin B values although they were slightly higher in the control subjects. All the other hormone levels were normal, including FSH.

James Huff (NIEHS, USA) You said that marijuana and amphetamine are oestrogenic and cause gynaecomastia. Do you know the mechanism of this effect, or is it simply an oestrogenic reaction? Our 2 year study on these agents (THC) suggested that they were somewhat protective against tumourigenicity, and were associated with reduced body weight, increased survival and reduced incidence of tumours compared to controls.

Giuseppe Chiumello Your results are very interesting. We do not have any evidence about the long term effect of THC.

Sabine de Muinck Keizer-Schrama (Rotterdam, The Netherlands) Did you follow up the girls in your 20 year study? They had a similar problem to the boys having developed thelarche.

Giuseppe Chiumello There was no difference between the exposed and control groups in final height, fertility and endocrine disorders. A slightly increased prevalence of acne and hirsutism was noted in exposed women.

Howard Kulin (Hershey, USA) Some years ago, in a controlled experiment, we treated normal prepubertal boys and girls with small doses of clomiphene citrate for 1 week: this drug regularly produced breast development within a few days (Kulin et al., Pediat Res 1972;6:162-71). Thus, prepubertal breast is extremely sensitive to oestrogens and it only takes a short time to produce a noticeable effect. Such information suggests that exposure to oestrogens from meat and other foods in the USA are probably at a very low level.

Giuseppe Chiumello There are other examples of induced gynaecomastia. Occasionally this occurs in children who ingest their mother's oral contraceptive pill and I am sure that small quantities of oestrogen can induce gynaecoymastia. However, the situation is quite different in Turner's syndrome and pituitary growth hormone deficiency in which oestrogen is given to induce puberty. In such circumstances, breast enlargement appears after weeks of treatment with a low dose of oestrogen. Probably our children received a high dose of oestrogen, or were exposed for a long time.

Why did you give clomiphene to normal children?

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Howard Kulin We were actually giving clomiphene as an anti-oestrogen in an attempt to stimulate gonadotrophins, but the breast is so sensitive that the weakly oestrogenic effect of this anti-oestrogen became apparent.

Andreas Daxenberger (Freising-Weihenstephan, Germany) What is the oral dose of oestradiol-170 necessary to cause gynaecomastia in children after acute or chronic administration? Is it possible that gynaecomastia can develop after ingestion of an implantation site of animals on one, two or three occasions?

Giuseppe Chiumello I do not know the dose required. It may be possible that ingestion of an implantation site can cause gynaecomastia, but I do not know for sure.

Unidentified Discussant According to your abstract gynaecomastia may occur in children exposed to oestrogen cream used by their parents. Would you please expand on that study.

Giuseppe Chiumello Recently it was described that 3 prepubertal boys presented with gynaecomastia after an indirect exposure to a custom-compounded preparation of oestrogen cream used by each child's mother. All 3 boys presented with gynaecomastia, elevated oestradiol levels, rapid changes in growth and advanced bone age.

Jean-Pierre Bourguignon (Liège, Belgium) Is there any evidence that the incidence of cryptorchidism and hypospadias is changing in the region of Italy where oestrogenic growth enhancers are used?

Giuseppe Chiumello We have no data available at present on cryptorchidism or hypospadias but we are studying the prevalence of gynaecomastia, precocious puberty and precocious thelarche because it is our impression that there has been an increase in the last few years. We have not been able to explain this so far, and at present we define it as being idiopathic.