Phytoestrogens in Soybean and Precocious Pubertal Development: Causality or Casuality?

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Abstract: *Introduction:* Data on the effects of phytoestrogens soy exposure on pubertal timing have been equivocal. We reported a case of a girl who had eaten only soy and derivatives for her first 9 years of life and presented clinical manifestation of precocious pubertal development.

Case presentation: A caucasian female infant, after 40 days of exclusive breastfeeding, was introduced to soy formula due to suspected milk protein allergy. Since then, the patient ate soy beverage and soy-based foods exclusively. At the age of 7 years and 9 months, the girl showed premature thelarche and pubarche. Advanced skeletal age was detected. Peak of LH after GnRH stimulation test was <5 mU/ml. At the age of 9 years, Tanner pubertal stage was 3, with a further advanced bone age; initial pubertal growth spurt and estrogenization of the external genitalia were also revealed. GnRH stimulation test produced a peak of LH 3.7 mU/ml. Other hormonal parameters resulted within normality ranges. Suspension of the intake of soy-based fozods was adopted. After 6- 12 months of follow-up, the physical examination and lab results were unchanged compared to the previous investigation, without progression of bone age. A slow progression of puberty was recorded. The patient had menarche at the age of 11 years and 1 month.

Conclusion: This case suggests that soybean compounds may play a key role, as an environmental factor, in the precocious pubertal development. Special attention to diet is mandatory in pediatric age in order to preserve a physiological development and future health.

Keywords: Phytoestrogens, Soybean, Precocious puberty, Soy beverage.

INTRODUCTION

Puberty is a critical phase of growth and development [1, 2]. The timing and patterning of pubertal events have been demonstrated to be subordinated to a lot of factors, including the exposition to endocrine disrupting chemicals (EDCs) [3, 4].

As well documented, EDCs can be natural or artificial. Phytoestrogen is a potential natural EDCs estrogenic composite found in plants. Soybean derivatives are the most important sources of phytoestrogen, containing high levels of isoflavones, which are a type of supplement produced almost exclusively by the bean family, having structural analogy to estrogen, being able to act both as an estrogen receptor agonist or antagonist [5, 7]. Animal studies provide evidence of the significant effects of phytoestrogen on sexual development, including impaired pubertal timing, changed estrous cycling and ovarian function, and modified hypothalamus and pituitary functions [7, 9].

Although animal studies have demonstrated the effects of phytoestrogens on reproductive organs, suggesting the potential correlation between their consumption and sexual development, human studies proving this relation are limited and not univocal [9, 17].

We report a case of a girl who had eaten only soy and derivatives for her first 9 years of life and presented clinical manifestation of precocious puberty, suggesting that phytoestrogen may provide some effects on the timing of puberty.

CASE PRESENTATION

She was born after a normal pregnancy, at 38 weeks of gestation. After 40 days of exclusive breastfeeding, the caucasian infant was introduced to soy formula due to suspected milk protein allergy.

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Since then, the patient has continued to eat only soy beverage and soy-based foods.

At the age of 7 years and 9 months, the girl showed premature thelarche and pubarche (stage 2 according to Tanner classification [18]. A history of familial precocious or early puberty was not reported. As evidenced in Table 1, advanced skeletal age of about 2 years compared to the chronological age was detected. Peak of LH following GnRH stimulation was <5 mU/ml. Thyroid and adrenal function were normal.

During monitoring, progression of pubertal signs was noted, Table 1. At the age of 9 years, pubertal stage was Tanner 3 [18]. And a further advanced bone age was confirmed (10 years and 9 months); initial pubertal growth spurt was also denoted. The patient presented hypertrichosis of the upper and lower limbs and estrogenization of the external genitalia. Pelvic ultrasound detected prepubertal aspect of internal genitalia. Laboratory investigation confirmed basal adrenal function, thyroid hormones and prolactin levels within the normal range. Tumoral markers (CEA, α-FP, -HCG) were negative. GnRH stimulation test was repeated, producing a peak of LH 3.7 mU/ml, Table 1. To complete the investigation, ACTH stimulation test was also performed, with evidence of normality.

Given that the current soy-based exclusive diet in substitution to cow milk was in relation to a suspected allergy, as referred by parents, an oral tolerance test for milk proteins was performed; the test excluded the presence of cow's milk protein allergy. Instead, the hydrogen breath test evidenced lactose intolerance.

Therefore, we recommended the interruption of soy beverage and *SOY*-based foods intake. Proximity to agricultural fields as proxy for environmental exposure to phytoestrogen or exposure to other endocrine disruptors were excluded.

After 6 and 12 months of follow-up, the physical examination and lab results were unchanged compared to the previous investigation, with no further progression of bone age.

The girl continued to exclude soy-based foods. A slow progression of puberty was recorded. The patient had menarche at the age of 11 years and 1 month.

DISCUSSION

The onset and progression of puberty is regulated by the neuroendocrine system [2]. The regular timing of puberty is crucial in psychological and physical development and can impact future health [13]. Girls with early puberty are at greater risk for psychiatric problems [19], social isolation, early sexual behavior, potential abuse by adults [19, 20]. Additionally, short adult stature and impact on reproductive function are other possible consequences of precocious puberty [1].

The interaction between genetic, endocrine, and environmental factors are crucial in the pubertal timing [1, 2]. Many reports have suggested a role of exogenous EDCs in the timing and development of puberty [9, 15]. EDCs are substances found in the environment, food sources, personal care and manufactured products that interfere with the regular endocrine system function.

Among the many types of EDCs, most exert estrogenic and/or anti-androgenic actions while a limited few exercise androgenic or anti-estrogenic effects [5-7, 22, 23]. Phytoestrogens, especially isoflavones, binding to estrogen receptors ERα and

Table 1: Features of the Girl during Monitoring

Features	Chronological Age at Evaluation			
	7 Years and 9 Months	9 Years	9 years and 6 Months	10 Years
Growth velocity/year (z-score) [34]	0.99	1.24	1.21	1.23
Tanner stage	2	3	3	3
Bone age	9 years and 6 months	10 years and 9 months	10 years and 9 months	11 years
LH peak (mU/ml)	3	3.7	nd	nd
Thyroid function	normal	normal	nd	normal
Adrenal function	normal	normal	nd	normal
Tumoral markers (CEA, -FP, -HCG)	negative	nd	nd	nd

nd=not detect.

ERβ, exert estrogen-like effects under particular conditions, having either agonist or antagonist activity based on the presence or absence of estradiol [5-7, 22, 23]. Thus, it appears plausible that EDCs might interfere with the normal pubertal development.

Of particular interest is the possible role on the pubertal timing of the phytoestrogens contained in soybean compounds, which are very common nowadays. Over the past two decades, soybean-based food has increased in popularity in many Western countries, not only in the diet but also in animal fodder. This increment in consumption is in part due to the health benefits; in fact, soybeans are a source of high-quality protein, omega-6 and omega-3, fatty acids, isoflavones and dietary fibers [24, 25].

Animal studies report that isoflavones given through diet or administered via subcutaneous injection during gestation or early life can lead sexual hormonal effects including early vaginal opening, irregular estrous cyclicity, and decreased activation of GnRH, the central regulator of the function of the pituitary-gonadal axis [27, 29]. These data suggest a plausible role in development of pubertal status in childhood; some nutrients contained in soy could be implicated in pubertal development and may synergistically impact the onset of puberty.

Since phytoestrogens can cross the placenta, the fetus is exposed to them through maternal dietary consumption and through breastfeeding after birth. The most important exposure to phytoestrogens occurs via soy-based formula feeding.

Even thought, early pubertal onset has been observed in girls exposed to other EDCs pre- and postnatally [30-33], overall data on the effects of early life exposure to soybean phytoestrogens and its effect on the timing of puberty have been equivocal [9-16].

Some authors [14, 15], reported that consumption of soy-based infant formula is not associated with early onset of puberty. On the other hand, the literature provides evidence that the exposure to soy isoflavones in early infancy may have lasting effects on later onset of puberty and reproductive development [9-16].

The effect of soy-based infant formula on pubertal development in humans has been shown to be associated with both very early (≤10 years) and late (≥15 years) menarche in a large cohort study [30-33]. Adget *et al*, reported that exposure to soy products in early infancy may contribute to a small increase in risk of menarche in early adolescence [17]. Seguia *et al*, reported that boys with higher soy isofavone intake had a 5-6 month earlier median age at pubarche compared to their low consuming counterparts [13].

These analyses legitimize our concerns about a possible over-exposure to soy-based products that could affect sexual maturation in children. As the number of girls sharing an anticipated onset of puberty is limited in comparison with normal age-matched ones eating the same foods, we hypothesize that some girls are more sensible to soy-based foods. The increase in cases of early puberty could be due to an increase in the amount of soy-based compound documented in recent years in the general population, as occurred in our patient.

Consequently, the question of whether phytoestrogens are beneficial or harmful to human health remains unresolved. The answer is likely complex and may depend on age, health status, and even the presence or absence of specific gut microflora. Clarity on this issue is needed as global consumption is rapidly increasing. Phytoestrogens are present in numerous dietary supplements and widely marketed as a natural alternative to estrogen replacement therapy. Actually, soy-based infant formulas are widely used as a source of nutrition for children in the first year of life and soy protein is added to many processed foods.

In conclusion, this case suggests that long-term soybean compounds may play a key role, as an environmental factor, in precocious pubertal development. Special attention to diet is mandatory in pediatric age in order to preserve a physiological development and future health.

STATEMENT OF ETHICS

The data for this case report were collected in accordance with the Declaration of Helsinki. The patient and her parents gave their informed consent to publish their case.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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