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REVIEW ARTICLE

Delayed Puberty Associated with Inflammatory Bowel Disease

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ABSTRACT

Delayed puberty frequently complicates the clinical course of young patients with inflammatory bowel disease, more often in Crohn's disease than ulcerative colitis. Undernutrition has been thought to be the main reason for delayed puberty in these patients. However, puberty may be delayed despite a normal nutritional status. Observations in patients with inflammatory bowel disease and in rats with experimental colitis suggest that inflammatory mediators may have a direct adverse influence, independent of undernutrition, on the onset and progression of puberty. Serum androgens are consistently reported to be reduced in patients with delayed puberty and inflammatory bowel disease. This reduction is not necessarily secondary to a reduction in gonadotrophins as serum concentrations of gonadotrophins have been reported to be normal or even increased in some studies. Management of delayed puberty involves calorie supplements to correct undernutrition and treatment of inflammation. Observations in boys with delayed puberty and controlled studies in experimental models of intestinal inflammation suggest that testosterone therapy can accelerate puberty. **(*Pediatr Res* 53: 205–210, 2003)**

Abbreviations
GnRH, gonadotropin releasing hormone
IBD, inflammatory bowel disease
NPY, neuropeptide Y
TNBS, trinitrobenzenesulphonic acid

Chronic inflammatory diseases such as Crohn's disease, ulcerative colitis, cystic fibrosis, and systemic juvenile rheumatoid arthritis may have serious consequences in young patients with respect to impairment of linear growth and delay in puberty (1–6). The psychological and social aspects of chronic inflammatory disease may be intensified during adolescence and psychological dysfunction associated with delayed puberty may be particularly common in males (7). Delay in the onset and progression through puberty may also have a deleterious effect on the normal pubertal growth spurt and contribute to the deficit in final adult height. In some cases, adulthood is characterized by short stature and sexual immaturity. This review will discuss the prevalence, etiology, and management of pubertal delay in adolescents with chronic inflammatory bowel disease.

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PHYSIOLOGY OF PUBERTY

Puberty marks the transition from a nonreproductive state into a reproductive state and is associated with widespread physical changes, including the development of pubic and axillary hair, the adolescent growth spurt, an increase in fat and muscle tissue, and in females, breast development and increase in hip width. The age of onset and the rate of progression through puberty vary among individuals and between ethnic populations. To assess the speed and extent of development, Tanner and colleagues developed a set of stages for axillary and pubic hair development, and breast and male genital development; these are widely used in clinical practice. The hormonal mechanisms initiating puberty are not fully understood. GnRH is synthesized and released in the arcuate nuclei and other nuclei of the hypothalamus. GnRH is transported *via* the hypophyseal portal capillaries to the gonadotrophs of the anterior pituitary gland, where it stimulates the synthesis and release of LH and FSH. In the testes, LH stimulates testosterone production from the interstitial or Leydig cells, which in turn acts locally to aid spermatogenesis and systemically to produce male secondary sex characteristics, anabolism, and the

maintenance of libido. FSH stimulates the Sertoli cells in the seminiferous tubules to produce mature sperm and the feedback hormone inhibin which decreases FSH secretion from the pituitary.

Different patterns of GnRH secretion are seen at different ages and, specifically during puberty, a diurnal rhythm of pulsatile GnRH secretion is seen. Before the onset of puberty, both LH and FSH are secreted in very small amounts and there is no apparent stimulation of the gonads. As puberty approaches, the amplitude of LH and FSH pulsatile secretion increases (and hence an increase in mean secretion rates and concentrations in peripheral blood) and the nocturnal rise in LH is amplified. The factors that act on the GnRH neurons to initiate puberty have not been identified, although recently several theories have been put forward to account for this change in secretion. According to the Frisch-Revelle hypothesis, a critical weight of 47.8 kg has to be reached before menarche will occur (8). A body fat level of 17% of body weight is also considered to be necessary for menarche to occur, and a 22% fat level to maintain regular menstrual cycles (9). Clinical observations suggest that these criteria do not strictly apply, but they emphasize the important interaction of nutrition and puberty. Leptin, the protein product of the *obese gene*, relays information about the state of the adipose tissue mass to the hypothalamic feeding centers (10). It has been suggested that leptin is the signal that relates adipose tissue mass to the timing of puberty. Specifically, infertility, a characteristic feature of leptin deficient (*ob/ob*) mice, is corrected by leptin administration. Furthermore, considerable changes in serum leptin are observed during puberty in animal and human studies. However, recent studies in rodents have shown that serum leptin concentrations do not show a significant increase until after the animals have become adults; the level of hypothalamic leptin receptor mRNA remains the same in juvenile, prepubertal, and postpubertal female rats; and treatment with leptin in fasted rats did not advance the timing of puberty onset in female mice compared with animals fed *ad libitum* (11). Taken together with previous data, these experiments suggest that leptin does not act as the primary trigger for the initiation of puberty but instead has a permissive action to allow puberty to proceed (12).

Animal studies suggest that the hypothalamic neurotransmitter NPY may also have a role in the onset of puberty. Central administration of NPY to prepubertal rats can delay sexual maturation by inhibiting secretion of GnRH. Juvenile female rats receiving chronic intracerebroventricular infusion of a specific NPY1 receptor antagonist experienced a quicker progression through puberty consistent with inhibition by endogenous hypothalamic NPY (13). Other hormones that may play a part in puberty are IGF-I and dihydroxyandrostenedione secretion from the adrenal cortex. The former by augmenting the pattern of sexual maturation once a pubertal pattern of gonadotropin secretion is established and the latter by aiding maturation of the GnRH neurons.

PUBERTY IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

Prevalence of Pubertal Delay. Delayed puberty and growth failure frequently complicate the clinical course of young patients with IBD, more often in Crohn's disease than in ulcerative colitis (14). Puberty is often delayed in patients with Crohn's disease in whom a remission has never been achieved or who had frequent relapses in the prepubertal period. In a study of young patients with Crohn's disease, menarche occurred at age 16 y or later in 73% of female patients in whom disease onset preceded puberty. In a few patients, menarche was delayed until the early 20s. In contrast, menarche occurred at 14 y or younger in all patients with juvenile-onset ulcerative colitis (14). In another study (2), the onset of puberty was taken as breast stage 2 in girls and testicular volume of 4 mL in boys. By these criteria, the mean age of onset of puberty was 12.6 y in young female patients with IBD compared with 11.1 y in healthy controls. In boys, the onset of puberty was 13.2 y in patients with IBD and 12.4 y in healthy controls (2). The duration of puberty may also be prolonged, particularly in patients with frequent disease relapses during this period (2). This study did not look separately at puberty in patients with Crohn's disease or ulcerative colitis. No study has addressed the effect of disease location (*e.g.* small bowel or large bowel Crohn's disease) on puberty onset.

Etiology and Pathogenesis of Pubertal Delay

Human studies. Patients with IBD are frequently underweight and undernutrition has been thought to be the main reason for delayed puberty in these children (3, 15–19). In a prospective study over 3 y, Motil *et al.* (20) found that 29–68% (depending on puberty stage) of young patients with Crohn's disease had weight-for-age measurements of $<90\%$ of expected and 10–24% had weight-for-height measurements of $<90\%$ of expected. During follow-up, 10–24% of the children had weight velocities of <1 kg/y. By comparison, undernutrition was less common in ulcerative colitis patients and 13–31% of patients had weight-for-age measurements of $<90\%$ of expected. The nutritional deficit results primarily from inadequate intake rather than from increased needs or losses. Disease-related anorexia may be profound and proinflammatory cytokines produced by the inflamed bowel are thought to be responsible. Experiments in rats with TNBS-induced colitis have implicated IL-1β in causation of anorexia, although in other inflammatory models tumor necrosis factor-α (TNF-α, previously called cachectin), IL-1β, and IL-6 have been shown to induce anorexia (21). Receptors for proinflammatory cytokines are expressed in the CNS, and it seems likely that peripherally produced cytokines induce CNS synthesis of cytokines, which in turn interact with specific hypothalamic feeding pathways to induce anorexia.

In children with Crohn's disease and growth failure, calorie intake has been documented to be only 43–82% of recommended values. In these patients, nutritional supplementation may be associated with onset of puberty and an increase in growth velocity (15–17). However, some patients with persistently active disease do not enter puberty despite the provision of adequate energy supplements, suggesting that factors in addition to undernutrition are implicated in the etiology of pubertal delay (2).

In patients with IBD, induction of a sustained remission is frequently associated with the onset of puberty. The most

impressive results are seen after surgical removal of active disease when the first signs of puberty often occur within 1 y of intestinal resection (2). Food intake is also likely to increase after resection of diseased bowel, and it is possible that the onset of puberty is, in part, related to improved nutrition. However, these observations also suggest that inflammatory mediators secreted by the inflamed gut may have a direct adverse influence, independent of undernutrition, on the onset and progression of puberty. With bowel resection and a reduction in inflammation, the inhibitory effects on puberty are removed. The rapid onset of puberty after bowel resection suggests that it is not merely related to the passage of time or age.

Observations in animals with experimental colitis. Rats with TNBS-induced colitis also have delayed puberty. This model, even in the early stages of evolution, is similar to human Crohn's disease, particularly with respect to T-cell activation and cytokine profile (22–24). We have examined the relative contribution of reduced food intake and inflammation to pubertal delay in this model (25). By using a group of healthy rats whose daily food intake was exactly matched to that of their pair in the colitic group, we have controlled precisely for the effects of undernutrition on the onset and progression of puberty in the colitic group. In the colitic group, this has allowed us to separate the effects of undernutrition (occurring equally in colitic and pair-fed groups) from inflammation (occurring only in the colitic group) on pubertal development. The onset of puberty was assessed in female rats by the age of vaginal opening and in male rats by full separation of the prepuce from the glans penis. The onset of estrous and the frequency of estrous cycling was determined in female rats by examination of vaginal smears for cellular morphology.

Induction of colitis with intrarectal administration of TNBS was associated with hypophagia and reduced weight gain. Undernutrition in healthy females (*i.e.* the pair-fed group) resulted in a delay in the onset of puberty (by 4.8 d) and progression of puberty (normal estrous cycles in only 38%) compared with controls (Table 1). However, onset of puberty was further delayed in the colitic group (1.4 d after the pair-fed group) with absence of normal estrous cycling in all rats. Similarly, onset of puberty was delayed in 57% of male rats with colitis but in only 28% of the pair-fed group compared with controls. In male rats, the weight of the accessory sex organs as a surrogate measure of testosterone effect was assessed at the end of the experimental period. Seminal vesicle and prostate weight was significantly less in the colitic group compared with pair-fed group (Table 1).

In summary, onset and progression through puberty is delayed in young patients with IBD and is related to undernutrition in some patients. However, observations in young patients with IBD suggest that other factors also play an etiological role. In some patients with IBD in whom adequate nutrition has been maintained, the presence of active disease is associated with pubertal delay. In rats with experimental colitis, inflammatory mediators potentiate the effects of undernutrition and result in a further delay in onset and progression through puberty. There have been no studies that have set out to determine which specific cytokines impact on puberty.

Endocrine Mediators of Pubertal Delay

The endocrine mechanisms responsible for pubertal delay associated with inflammatory disease are incompletely understood. From the preceding discussion, the hypothalamic-pituitary-gonadal axis is under the influence of both nutritional and inflammatory mediators associated with intestinal inflammation. In both animals and humans, food deprivation and a reduction in body weight are associated with reduced activity of hypothalamic neurons producing GnRH, and hence pituitary gonadotropins, and this is thought to mediate pubertal delay (26, 27). However, in humans there is no simple model of undernutrition and confounding variables influence studies in underweight patients. For example, in patients with anorexia nervosa, basal and GnRH-stimulated plasma concentrations of gonadotropins are reduced for up to a year after normalization of body weight, suggesting that hypogonadism is caused by factors other than nutritional deficiency, including psychological abnormalities (28, 29). In rodents, the gonadotropin response to undernutrition has usually only been assessed after periods of extreme calorie deprivation (30–32) and the results of these studies may not necessarily be applicable to lesser degrees of undernutrition that occur with chronic inflammatory disease. A mechanism other than reduced gonadotropin secretion is suggested in undernutrition by the observation that, in peripubertal rats, gonadotropin secretion was normal but seminal vesicle weight was reduced after 4 d of food restriction (33). Rapid weight loss in IBD patients has been associated with prepubertal levels of circulating sex steroids despite previous evidence of pubertal progression (34).

Table 1. *Age in days of onset of puberty in female and male rats, the percentage of female rats who had normal oestrous cycles, and the weight of seminal vesicles and ventral prostate in male rats*

	Females		Males		
	Onset of puberty (age in days)	Normal estrous cycle (%)	Delayed puberty (%)*	Seminal vesicle weight (mg)	Ventral prostate weight (mg)
Controls	35.6 ± 1.4	93	6	131.7 ± 45.5	104.9 ± 24.9
Colitis	41.8 ± 3.2†‡	0¶	57	46.4 ± 19.1†§	45.1 ± 26.4†§
Pair-fed	40.4 ± 3.2†	42†	28	83.6 ± 32.1†	78.6 ± 17.5†

Values are the mean ± SD. Onset of puberty was assessed in female rats by the age in days at vaginal opening and in male rats by the age in days of full separation of the prepuce from the glans penis.

* Most of the male colitic group had not entered puberty at the end of the experiment, and the results are therefore expressed as the proportion that had delayed puberty, defined as the mean of +2 SD of healthy free-feeding controls. Adapted from ref. 25.

† $p < 0.05$ *vs* healthy, free-feeding controls; ‡ $p = 0.09$ *vs* pair-fed; § $p < 0.05$ *vs* pair-fed; ¶ $p = 0.06$ *vs* pair-fed.

McCaffrey *et al.* (35) reported reduced urinary gonadotropins in patients with Crohn's disease and restoration of normal concentrations when the disease was in remission. In contrast, Chong *et al.* (36) reported that the gonadotropin response to GnRH was appropriate for pubertal stage in 14 children with active Crohn's disease and growth delay. Neither of these studies controlled for nutritional deficit and it is not known whether the reduced hormone levels found in the study by McCaffrey *et al.* were related to undernutrition, inflammatory mediators, or other factors.

It is difficult to accurately control for calorie intake and nutritional status in patient studies. We have measured serum sex steroids and gonadotropins in rats with TNBS-induced colitis and compared the results with healthy controls and pair-fed rats and also related serum concentrations to puberty stage. In colitic and pair-fed groups, although the onset and progression of puberty was delayed, plasma concentration of gonadotropins was similar to that seen in healthy free-feeding controls (25). *In vivo* secretion of pituitary gonadotropins was not measured, and it is possible, although it seems unlikely on the basis of the plasma concentrations, that amplitude or frequency of pulses of gonadotropin secretion was reduced in colitic rats. Possible influences on GnRH secretion in colitis are leptin and IGF-I, which are reduced in humans and animals with intestinal inflammation as a result of undernutrition (1).

In male rats with TNBS-colitis, plasma concentrations of testosterone were significantly ($p = 0.02$) reduced at two time points to 40% and 55%, respectively, of control values. However, concentrations were similar in colitic and pair-fed groups. Plasma concentrations of 17β-estradiol were also lower in colitic and pair-fed groups compared with healthy controls, although this just failed to reach statistical significance ($p = 0.08$). Taken together, these results suggest that the delay in puberty onset and progression in TNBS-colitis is not mediated by reduced production of gonadotropins. The reduction in plasma concentrations of testosterone in colitic rats is consistent with the human data and suggests that inadequate production of androgens may contribute to the delay in puberty. Undernutrition seems to be the main determinant of reduced testosterone concentrations as levels were similar in colitic and pair-fed groups. The delay in puberty in colitic rats relative to pair-fed rats may be related to resistance to circulating testosterone. However, any resistance must only be partial as exogenous administration of testosterone accelerates puberty in male rats with colitis.

It is not known which specific cytokines mediate the pubertal delay associated with Crohn's disease or TNBS-colitis. TNF-α plays a central role in the pathogenesis of Crohn's disease and therefore may play a role in delayed puberty that is mediated, in part, by the inflammatory response. *In vitro*, studies suggest that this may indeed be the case. TNF-α decreased androgen receptor protein and mRNA levels in a prostate cancer cell line and also inhibited the ability of dihydrotestosterone to induce cell proliferation and activate the prostate-specific antigen gene promotor (37). In contrast, another key cytokine, IL-6, up-regulated androgen receptor expression and activated androgen receptor-mediated gene expression in this cell line (38, 39).

Management of Delayed Puberty

From the preceding discussion of the etiology of pubertal delay, it seems likely that in IBD patients' optimal management involves reduction of intestinal inflammation and also calorie supplements to correct undernutrition. In patients with Crohn's disease, exclusive enteral feeding with elemental or polymeric feeds for 8 wk combines nutritional treatment with specific antiinflammatory effects (40), and is thus ideal for patients with growth failure and pubertal delay. At our institution, enteral nutrition is used as first-line therapy in inducing a remission in acute Crohn's disease. However, the rate of relapse after enteral nutrition is about 50% at 12 mo. Corticosteroids are usually reserved for children with severe or refractory disease because of the potential adverse effects associated with these agents, particularly on linear growth. It is not known whether the doses used in the management of Crohn's disease also delay the onset and progression of puberty, but arrested puberty has been described in patients with Cushing's disease (41). Maintenance of remission, particularly during periods of rapid growth, *e.g.* during puberty, is a key aim of management. This can be achieved with mesalazine derivatives, continuation of elemental or semi-elemental nutrition without restriction of normal diet, and 6-mercaptopurine (6-MP) and its prodrug azathioprine (42, 43). Significant delay and/or growth failure persisting during medical management are relative indications for surgery in young patients with IBD. Intestinal resection is associated with the onset of normal puberty and, providing remission is maintained for the duration of puberty, the height increment will enable young patients to achieve some degree of catch-up of growth potential (2).

Animal studies suggest that androgen therapy is efficacious in promoting pubertal development even in the presence of active inflammation and undernutrition. In rats with TNBS-colitis, daily subcutaneous administration of testosterone increased plasma concentrations of testosterone to three- to four-fold those of healthy controls and completely restored weight of the accessory sex organs to control values. The onset of puberty was also similar to that of healthy free-feeding controls. Testosterone treatment had no effect on food intake, body weight, or severity of colonic inflammation (25).

Sex steroid therapy has a place in the management of delayed puberty in chronic illness. Many patients, particularly boys, are psychologically disturbed by their failure to enter or progress through puberty. There are no controlled studies of testosterone use in IBD, however, observations from other inflammatory diseases suggest a potentially useful role if puberty is still delayed despite optimizing nutrition and treating the inflammation. Puberty is frequently delayed in young patients with cystic fibrosis and rheumatoid arthritis and, similar to IBD, puberty can be delayed in cystic fibrosis despite a normal nutritional status (6, 44–49). In young patients with arthritis or cystic fibrosis, the endocrine profile is similar to that in patients with IBD or rats with experimental colitis. Clinical studies have consistently shown a reduction in serum androgens, and serum concentrations of gonadotropins are variably reported to be increased or reduced (49–53). Depot testosterone for 3–6 mo can induce helpful virilization and growth

acceleration in affected boys (54). Landon and Rosenfeld (45) assessed the efficacy of short-term testosterone therapy in promoting growth in five male adolescents with cystic fibrosis and delayed puberty. Growth rate increased from an entry mean of 2.2 cm/y (range, 0–4 cm/y) to 7.2 cm/y (3–10 cm/y). The authors concluded that testosterone was a safe and effective means of improving growth rate in male adolescents with cystic fibrosis.

In young patients with IBD, our current therapy for males consists of a single 3- to 6-mo course of intramuscular testosterone ester (enanthate or cypionate) therapy in a dose of 100–125 mg/mo. Girls may be treated with ethynylestradiol, 4–6 μg/d, for the same time period. In healthy boys with constitutional delay of puberty, testosterone therapy would be expected to increase growth velocity from <5 cm/y to >8 cm/y. It is possible that, in the presence of active chronic inflammation, the response may be inferior to this. However, in our pediatric IBD clinic, encouraging results from this therapy have been seen with noticeable improvement in psychological status.

There have been concerns that administration of sex steroids will compromise final adult height because of premature closure of the epiphyses. Theoretically, there may be a potential advantage for final adult height in normal subjects of a delay in puberty or of a prolonged puberty. This hypothesis assumes a normal height velocity before and throughout the adolescent growth spurt. In a patient with chronic illness, this assumption cannot be made. We know in Crohn's disease that an exacerbation of active disease may suppress height velocity to well below normal values. Under these circumstances, one cannot assume that delaying puberty will improve final height. However, if treatment is given it would seem prudent to start with a low dose of sex steroids.

SUMMARY

Puberty is frequently delayed in young patients with IBD, more often in Crohn's disease than ulcerative colitis. Observations in patients with IBD and controlled experiments in rats with TNBS-induced colitis suggest that inflammatory mediators adversely influence the onset and progression of puberty, or at least potentiate the effects of undernutrition. The hormonal mechanisms leading to the delay in puberty are incompletely understood. However, it is clear from the animal studies and some of the human studies that puberty is not simply delayed as a result of inadequate production of gonadotropins. Serum concentrations of sex steroids are reduced and results in the rat TNBS-colitis model suggest that this is mainly as a result of undernutrition. However, it seems likely that inflammatory cytokines lead to a degree of resistance to testosterone that can be overcome by exogenous administration of testosterone.

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