Alterations in Pubertal Timing following Therapy for Childhood Malignancies

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Abstract

The onset of puberty marks a time of rapid linear growth, sexual development, and transition from childhood to maturity. As a result, children experience the appearance of secondary sexual characteristics, the adolescent growth spurt, and the establishment of fertility. This occurs as a consequence of central nervous system (CNS) maturation and release of pituitary gonadotropins resulting in stimulation of gonadal end organs (testis/ovaries) [1]. The diagnosis and treatment of a childhood malignancy prior to the onset of puberty has the potential to profoundly impact the timing and the tempo of puberty. CNS tumors located in the hypothalamic-pituitary (H-P) region, surgical resection in this location, and exposure to CNS radiotherapy are all associated with both precocious and delayed puberty. Also, chemotherapy and radiation can directly damage the gonads, which can result in absent, arrested, or delayed puberty. As a consequence of these alterations of pubertal timing, both male and female survivors of childhood cancer may be at risk of adult short-stature, decreased bone-mineral density, absent or incomplete sexual development, and ultimately, reduced rates of fertility. Appropriate and timely assessment of survivors at high risk of alterations in pubertal development will enable the identification of patients who would benefit from early medical intervention.

The onset of puberty marks a time of rapid linear growth, sexual development, and transition from childhood to maturity. As a result, children experience the appearance of secondary sexual characteristics, the adolescent growth spurt, and the establishment of fertility. This occurs as a consequence of central nervous system (CNS) maturation and release of pituitary gonadotropins resulting in stimulation of gonadal end organs (testis/ovaries) [1]. The diagnosis and treatment of a childhood malignancy prior to the onset of puberty has the potential to profoundly impact the timing and the tempo of puberty. CNS tumors located in the hypothalamic-pituitary (H-P) region, surgical resection in this location, and exposure to CNS radiotherapy are all associated with both precocious and delayed puberty. Also to be considered, chemotherapy and radiation exposure to
the gonads can result in premature gonadal failure that may be clinically evident as absent, delayed, or arrested puberty. As a consequence of these alterations of pubertal timing, survivors of childhood cancer may be at risk of adult short stature, decreased bone mineral density, absent or incomplete sexual development and ultimately, reduced rates of fertility. Currently, 80% of children treated for childhood malignancies will become long-term survivors of their cancer [2, 3]. Therefore, understanding which patients are at high risk of alterations in pubertal timing is essential. Appropriate and timely assessment of these patients will allow identification of survivors who would benefit from early medical intervention.

**Normal Puberty**

The onset of puberty in females is heralded by an increase in height velocity with simultaneous maturation of the glandular and connective tissue of the mammary gland (thelarche). Adrenarche, the growth of pubic and axillary hair, is a phenomenon distinct from breast development as it is largely controlled by androgens secreted by the adrenal gland. Nonetheless, pubic hair development generally parallels breast development. The onset of menses typically correlates with Tanner stage 4 breast development and occurs at an average age of 12.4 years [4]. Several large epidemiologic investigations in the United States, using both representative population samples and large convenience samples, have concluded that a secular trend towards earlier sexual development in females has occurred over the last few decades [5]. Moreover, there appear to be differences between girls of various racial and ethnic backgrounds. For example, non-Hispanic Black girls appear to mature earlier than their Hispanic and Caucasian counterparts [4]. However, while it appears that girls are maturing earlier than they did several decades ago, the age at menarche appears to have changed very little if at all [5]. A recent British study with a more homogeneous population has also shown minimal change in the age of menarche over the past few decades [6]. It has been postulated that this trend to earlier onset of puberty may be related to the recent increase in the rates of childhood obesity.

Across most studies, age at onset of puberty follows a normal distribution with a standard deviation of approximately 1 year. Routinely, children with onset or delay of puberty more than 2 standard deviations from the mean should be considered for medical evaluation of precocious or delayed onset of puberty. For girls, transition from Tanner stage 1 to 2 of breast development is defined by the development of a breast bud and occurs at a mean age of 10 years [7]. Following this standard, females who develop breast buds before age 8 are classified as having precocious puberty, while delayed puberty is defined as no evidence of breast development by age 13.
Among males, the beginning of puberty is marked by an increase in testicular volume followed shortly by the development of pubic hair and growth and maturation of the penis. Finally, peak height velocity occurs between Tanner stages 4 and 5 of genital development. The mean onset of puberty in males is 11 years with limits at 2 standard deviations extending the normal range of onset to 9–14 years of age. Testicular enlargement or other signs of virilization before age 9 are considered precocious. Similarly, a male with no evidence of testicular enlargement by age 14 should be evaluated for delayed onset of puberty. It is important to note that testicular enlargement is largely secondary to growth of the sperm-producing seminiferous tubules, which are very susceptible to damage by various chemotherapeutic agents (e.g. alkylating agents) and external radiation. Thus, for many male cancer survivors, testicular size is not a reliable marker of pubertal maturation as the testes may remain small despite the onset of puberty.

The control mechanisms involved in the timing of the onset of puberty are poorly understood. However, an increase in the pulsatile rate of release of GnRH from the medial basal hypothalamus is the initiating factor for the onset of puberty. In response to this increased rate of release of GnRH, the anterior pituitary releases LH and FSH in a likewise pulsatile manner. The end result is stimulation of the gonads by these gonadotropin pulses, resulting in production and release of gonadal sex steroids. During childhood, the CNS exerts restraint on the hypothalamic GnRH-secreting neurons and pulsatile release of GnRH is suppressed. During CNS maturation, however, these poorly understood restraining forces subside and hypothalamic release of GnRH is reactivated, allowing the normal onset of puberty [1].

**Early Puberty**

Precocious puberty can occur as a result of either tumor or radiotherapy-induced disruptions of H-P axis regulation of pubertal timing. Precocious puberty can be a presenting symptom of a CNS tumor in both males and females [8, 9]. Among 197 girls and 16 boys who presented with precocious puberty in a British series, 2 girls and 1 boy were subsequently found to have a CNS tumor [9]. In a separate series of 100 children with precocious puberty due to a CNS lesion, 45 had optic pathway gliomas or astrocytomas; 8 presented with precocious puberty, while the other 37 developed symptoms following treatment of their tumor [10]. Optic pathway gliomas, which most commonly present in the anterior half of the optic pathway, are a subgroup of astrocytomas that place a patient at particular risk of early puberty due to their proximity to the H-P axis. Other CNS lesions associated with precocious puberty include benign lesions such as hamartomas and cysts, and more rarely, craniopharyngiomas [10, 11]. Craniopharyngiomas are benign,
slow-growing tumors thought to arise from Rathke’s pouch (epithelial remnant of
the craniopharyngeal duct) [12]. These lesions can all occur in the region of the
H-P axis and disrupt hormonal regulation due to direct mass effect and/or hydro-
cephalus secondary to ventricular system obstruction. The result is an increased
risk of early (but also delayed) pubertal onset. Lastly, germ cell tumors, including
those arising within and outside the CNS, also can cause precocious puberty, pri-
marily in males, through the production of hCG [13].

Effects of Central Nervous System Radiation

Overall among childhood cancer patients, central precocious puberty occurs most
commonly following radiotherapy to the H-P region. Among patients with CNS
tumors outside the H-P axis who received radiotherapy (doses 25–72 Gy), both
male and female survivors were on average more likely to start puberty earlier (in
some reports >1.5 years earlier) compared with population or reference norms
[14–16]. Younger age at exposure was also associated with earlier onset of puberty
in both sexes [14, 15]. However, cranial radiotherapy doses of 30–40 Gy are also
associated with an increased risk of inducing gonadotropin deficiency, resulting in
failure of pubertal maturation [17, 18].

Early puberty, at least among girls, has also been seen following exposure to
lower doses of cranial radiotherapy given as part of treatment for childhood acute
lymphoblastic leukemia (ALL). Historically, even in the absence of detectable
CNS leukemia, cranial radiotherapy was used widely to prevent subsequent CNS
recurrences. Although cranial radiotherapy has largely been replaced by high dose
methotrexate and intrathecal chemotherapy in many current treatment protocols,
around 10–15% of ALL patients still receive cranial radiation, usually between 12
and 25 Gy [19]. A report by Quigley et al. [20] in 1989 found that among Australian
ALL survivors, 24 Gy cranial radiotherapy was associated with earlier pubertal
onset and progression to menarche in girls when compared with siblings and pop-
ulation norms. Pubertal onset in boys was not affected, although boys were noted
to have smaller testicular sizes and low/absent germ cells in testicular biopsies done
at completion of therapy, despite receiving no gonadal radiation [20]. The find-
ing that various pubertal milestones among girls may occur up to a year earlier
than expected following 24 Gy cranial radiotherapy has since been confirmed by
additional studies [21–24]. However, studies have not shown pubertal onset among
boys to be significantly affected, although subtle differences in the magnitude or
duration of the pubertal growth spurt may occur [22, 23].

Relatively few ALL patients currently receive cranial radiotherapy, and in those
who do, a dose of 18 Gy now is preferentially used over 24 Gy [19]. Several stud-
ies have shown that this lower dose still is associated with earlier than expected