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Spina Bifida Guideline

Central precocious puberty in spina bifida children: Guidelines for the care of people with spina bifida

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Abstract. Children with spina bifida are at greater risk of developing central precocious puberty (CPP) compared to others. Therefore, early recognition and timely referral for further evaluation by a pediatric endocrinologist allows appropriate management that reduces the impact of CPP. This article discusses the diagnosis and management of CPP in children with spina bifida. This guideline was developed for SB Transition Healthcare Guidelines from the 2018 Spina Bifida Association's Fourth Edition of the Guidelines for the Care of People with Spina Bifida.

Keywords: Spina bifida, myelomeningocele, neural tube defects, precocious puberty, GnRH analog

1. Introduction

Central precocious puberty (CPP) is defined as the premature activation of the hypothalamic-pituitary-gonadal (HPG) axis, which leads to the early appearance of secondary sexual characteristics. Traditionally, CPP is considered to be the onset of pubertal changes before age eight years in girls and nine years in boys. However, to be more precise, it is the onset of pubertal changes at an age younger than the accepted norm for that individual's ethnicity and race.

The diagnosis of CPP should be considered in girls with progressive breast development, and is often accompanied by other signs of increased estrogen such as the maturation of the nipples and areolae, or vaginal secretions. Pubic or axillary hair and adult body odor may or may not be present. Findings in boys include bilateral testicular enlargement (volume $\geqslant$ 4 mL or length $>$ 2.5 cm) often with penile enlargement, axillary/pubic hair, body odor, or behavioral changes. In both sexes, growth acceleration leads to increased height percentiles and advanced bone age (often more than 2 standard deviations greater than chronologic age). This acceleration of skeletal maturation may lead to permanent loss of adult height.

Children with myelomeningocele (MMC) have an increased incidence of CPP. Previous studies reported that the prevalence of CPP in girls with MMC is as high as 50%. In contrast, estimates in boys range from 10–30% [1–3]. While the exact causative mechanism in children with MMC is not known, several studies demonstrated an association with hydrocephalus, which may alter HPG axis function [4,5]. Additionally, evidence shows that increased perinatal intracranial pressure and brainstem malformations, i.e. Chiari II malformations, are influential prognostic factors for the development of CPP.

In addition to short stature, psychosocial consequences of precocious puberty may arise related to in-

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Table 1
Clinical questions that informed the puberty and precocious puberty guidelines

Age group	Clinical questions
0–11 months	How often should weight and length be measured in ages 0–11 months?
1–2 years 11 months	What effect does hydrocephalus have on early onset of puberty?
3–5 years 11 months	1. What is the best practice for detection and management of early puberty? 2. Should every child with early signs of puberty be referred to an endocrinologist?
6–12 years 11 months	1. Does intervening in pubertal development affect a child's self-perception? 2. What is the psychological impact on the initiation of puberty on the parent/caregiver versus the child?
13–17 years 11 months	How does puberty affect the self-perception of the 13–17-year old with spina bifida?
18+ years	1. How has completing puberty affected the individual's relationships with others? 2. Has the individual's self-perception changed as a result of completing puberty?

creasing differences from peers and self-hygiene problems from early menses, especially in cognitively impaired children. Therefore, children with spina bifida should be examined regularly to ensure early diagnosis of precocious pubertal development, as CPP adds additional burden on affected children and their caregivers.

2. Guidelines goals and outcomes

Primary

– Timely assessment of the onset of puberty, identification and counseling for normal variants of puberty, and appropriate referral and management of precocious puberty.

Secondary

– Decreased risk of unwanted consequences of precocious puberty among children with spina bifida.

3. Methods

The methodology for the development of these guidelines was reported by Dicianno et al. [6]. A small multidisciplinary working group was recruited and convened based on expertise to review previous clinical care guidelines, choose pertinent topics, agree upon outcome measures, and develop clinical questions and guidance to address this topic for optimal care for people with spina bifida. These questions were vetted by a panel of experts from the Spina Bifida Association and ranked by importance. A literature review pertinent to the topic was conducted from the mid-1970s through 2002 and updated with works published from 2002 to 2015. Two levels of review were conducted. The first level consisted of review of titles and abstracts to eliminate articles that did not address the clinical questions for those guidelines. The second level of review involved reading the full text of the article to determine if the work should be included in the literature review for the development of these guidelines. The next phase of guideline development was the drafting of the guidelines with introduction, outcomes, clinical questions (Table 1), guidelines, and research gaps. These drafts were presented to a committee of working group chairs who served as reviewers and editors. The subsequent draft was then submitted for review and comment at a meeting of all guideline writing participants at a national Spina Bifida Association Meeting in March 2017. Nominal Group Technique was used to solicit feedback on individual guidelines [7–11]. This technique allowed for expert opinion to be included for those guidelines where medical evidence was non-existent or not robust. Participants in this review were able to rate the proposed guidelines and provide feedback. Once changes were incorporated, a review was then conducted by a panel of six experts in the field for consistency, redundancy, disability-sensitive language, and clarity. The final review was performed by the Spina Bifida Association Steering Committee and once approved the guidelines were sent for copyediting [12].

4. Results

The Puberty and Precocious Puberty guidelines (Table 2) seek to facilitate identification of children with abnormal pubertal maturation and promote timely referral for further evaluation and treatment if needed. The guidelines recommend examining children at regular intervals and thoroughly documenting physical examination findings so that changes may be tracked over time. This includes not only length/height and weight, but also the presence of any pubertal changes, such as breast development, genital maturation, or the presence of pubic or axillary hair. The guidelines emphasize careful communication with families regarding the findings and concerns. Although precocious puberty is common in children with spina bifida, delayed puberty

Table 2
Puberty and precocious guidelines

Age group	Guidelines	Evidence
0–11 months	1. Monitor and document weight and length closely at every health supervision visit. Measure length with a length measuring board.	Guidelines for Health Supervision of Infants, Children, and Adolescents [13]. Clinical consensus
	2. Perform a complete physical exam, including of the breasts and genitalia, at each health supervision visit. Offer for the exam to be completed by a provider of the same sex if the child and/or family is more comfortable with a same-sex provider.	Guidelines for Health Supervision of Infants, Children, and Adolescents [13]. Clinical consensus
	3. Document all positive and negative findings of the physical exam.	Clinical consensus
	4. Discuss the outcomes of the evaluation with the parents or caregivers and ask them if they have any concerns.	Clinical consensus
	5. Refer the child to a pediatric endocrinologist if abnormal signs of puberty are observed.	Clinical consensus
1–2 years 11 months	1. Monitor and document weight and height velocity closely at every health supervision visit. Measure length using a length measuring board.	Guidelines for Health Supervision of Infants, Children, and Adolescents [13]. Clinical consensus
	2. Perform a complete physical exam, including of the breasts and genitalia, at each health supervision visit. Offer for the exam to be completed by a provider of the same sex if the child and/or family is more comfortable with a same-sex provider.	Guidelines for Health Supervision of Infants, Children, and Adolescents [13]. Clinical consensus
	3. Document all positive and negative findings of the physical exam.	Clinical consensus
	4. Discuss the outcomes of the evaluation with the parents or caregivers and ask them if they have any concerns.	Clinical consensus
	5. Refer the child to a pediatric endocrinologist if abnormal signs of puberty are observed.	Evaluation and Referral of Children with Signs of Early Puberty [14]. Clinical consensus
3–5 years 11 months	1. Monitor and document weight and height velocity closely at every health supervision visit. Measure height (if possible) using a stadiometer. Often there may be difficulty assessing height due to inability to stand, scoliosis or contractures. In these cases, arm span or another appropriate parameter may be used. Care should be taken to use the same parameter at subsequent visits.	Guidelines for Health Supervision of Infants, Children, and Adolescents [13]. Clinical consensus
	2. Perform a complete physical exam, including of the breasts and genitalia, at each health supervision visit. Offer for the exam to be completed by a provider of the same sex if the child and/or family is more comfortable with a same-sex provider.	Guidelines for Health Supervision of Infants, Children, and Adolescents [13]. Clinical consensus
	3. Document all positive and negative findings of the physical exam.	Clinical consensus
	4. Discuss the outcomes of the evaluation with the parents or caregivers and ask them if they have any concerns.	Clinical consensus
	5. Refer the child to a pediatric endocrinologist if abnormal signs of puberty are observed. Abnormal signs could include progressive breast development over a 4- to 6-month period of observation or progressive penis and testicular enlargement, especially if accompanied by rapid linear growth. Children exhibiting these true indicators of early puberty need prompt evaluation by an appropriate pediatric endocrinologist.	Evaluation and Referral of Children with Signs of Early Puberty [14].
6–12 years 11 months	1. Monitor and document weight and height velocity closely at every health supervision visit. Measure height (if possible) using a stadiometer. Often there may be difficulty assessing height due to inability to stand, scoliosis or contractures. In these cases, arm span or another appropriate parameter may be used. Care should be taken to use the same parameter at subsequent visits.	Guidelines for Health Supervision of Infants, Children, and Adolescents [13]. Clinical consensus
	2. Perform a complete physical exam, including of the breasts and genitalia, at each health supervision visit. Offer for the exam to be completed by same provider of the same sex if the child and/or family is more comfortable with a same-sex provider.	Guidelines for Health Supervision of Infants, Children, and Adolescents [13]. Clinical consensus
	3. Document all positive and negative findings of the physical exam.	Guidelines for Health Supervision of Infants, Children, and Adolescents [13]. Clinical consensus

Table 2, continued

Age group	Guidelines	Evidence
	4. Discuss the outcomes of the evaluation with the parents or caregivers and ask them if they have any concerns.	Clinical consensus
	5. Refer the child to a pediatric endocrinologist if abnormal signs of puberty are observed. Abnormal signs could include progressive breast development over a 4- to 6-month period of observation or progressive penis and testicular enlargement, especially if accompanied by rapid linear growth. Children exhibiting these true indicators of early puberty need prompt evaluation by an appropriate pediatric endocrinologist.	Evaluation and Referral of Children with Signs of Early Puberty [14].
	6. Consider a referral to a mental health professional if the child is having psychosocial issues with his or her growth or development.	Clinical consensus
13–17 years 11 months	1. Monitor and document weight and height velocity closely at every health supervision visit. Measure height (if possible) using a stadiometer. Often there may be difficulty assessing height due to inability to stand, scoliosis or contractures. In these cases, arm span or another appropriate parameter may be used. Care should be taken to use the same parameter at subsequent visits.	Guidelines for Health Supervision of Infants, Children, and Adolescents [13]. Clinical consensus
	2. Perform a complete physical exam, including of the breasts and genitalia, at each health supervision visit. Offer for the exam to be completed by a provider of the same sex if the child and/or family is more comfortable with a same-sex provider.	Guidelines for Health Supervision of Infants, Children, and Adolescents [13]. Clinical consensus
	3. Document all positive and negative findings of the physical exam.	Clinical consensus
	4. Discuss the outcomes of the evaluation with the parents or caregivers and ask them if they have any concerns.	Clinical consensus
	5. Refer the child to a pediatric endocrinologist if there is clear evidence of abnormal timing, tempo, or sequence of pubertal development.	Evaluation and Referral of Children with Signs of Early Puberty [14]. Clinical consensus
	6. Consider a referral to a mental health professional if the child is having psychosocial issues with their growth or development.	Clinical consensus
18+ years	1. Perform a complete physical exam, including of the breasts and genitalia, at each health supervision visit. Offer for the exam to be completed by a provider of the same sex if the adult is more comfortable with a same-sex provider.	Guidelines for Health Supervision of Infants, Children, and Adolescents [13]. Clinical consensus
	2. Document all positive and negative findings of the physical exam.	Guidelines for Health Supervision of Infants, Children, and Adolescents [13]. Clinical consensus
	3. Discuss the outcomes of the evaluation with the patient and with parents or caregivers, if appropriate, asking them if they have any concerns.	Clinical consensus
	4. Consider a referral to a mental health professional if the individual is having psychosocial issues with their growth or development.	Clinical consensus
	5. Discuss sexual health issues and make appropriate referrals to urologists, gynecologists or other sub-specialists including endocrinologists, adolescent medicine, genetics or others, as clinically appropriate.	Spina Bifida Association. Men's Health. Guidelines for the care of people with spina bifida. 2018 [15]. Spina Bifida Association. Sexual Health and Education. Guidelines for the care of people with spina bifida. 2018 [15]. Spina Bifida Association. Women's Health. Guidelines for the care of people with spina bifida. 2018 [15]. Clinical consensus

or even hypogonadism can rarely occur as well. Thus, the provider should ensure that pubertal development in adolescents has occurred appropriately.

5. Discussion

When dealing with a child who might be maturing at an early age, it is important to have a good understanding of normal pubertal timing. Historically, puberty was believed to start between 8–13 years in girls and 9–14 years in boys [16]. Current evidence indicates that the age at menarche, a predictor of pubertal growth in girls, has decreased in Europe and the U.S. over the last century, with white girls currently experiencing the onset of breast development at an average age of 10 years

and African-American girls between the ages of 8 and 9 years [17]. Data are mixed regarding secular changes in pubertal timing for boys. The causes for the change are unclear. However, as the genetic pool remains relatively constant over time, changes in timing are assumed to be linked to both environmental and social influences. Improved overall health, obesity, endocrine disrupting chemicals, and maternal exposures are also identified as possible causative factors [18].

Puberty results from the activation of a multifaceted neuroendocrine system, but the primary mechanism for this is unclear. Although the development of the hypothalamic-pituitary-gonadal (HPG) axis takes place throughout embryogenesis, the process remains suppressed until puberty, with the exception of the first few months of life. When the hypothalamus starts increasing its pulsatile secretion of gonadotropin releasing hormone (GnRH), puberty is activated. This pulsatile GnRH secretion is regulated by a complex neuroendocrine mechanism that involves various inhibitory and stimulatory inputs. Currently, there is growing evidence showing that kisspeptin-secreting neurons in the arcuate nucleus of the hypothalamus produce dynorphin and neurokinin B to induce pulsatile GnRH secretion, and the earliest detectable biochemical change seen in puberty is increased hypothalamic kisspeptin production. In CPP, the pathophysiologic processes causing the initiation of puberty generally remain unknown, although some patients have activating mutations of the kisspeptin receptor, while others have inactivating mutations in MKRN3 which encodes a protein involved in maintaining the prepubertal state [18–20]. The process of HPG activation is called gonadarche. Hypothalamic GnRH induces the synthesis of the pituitary gonadotropins: luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH stimulates the testes to secrete testosterone, while LH and FSH are both required for ovarian estradiol production. Additionally, FSH promotes spermatogenesis and oocyte growth and increases gonadal size. Further, estradiol in girls causes progressive breast development (known as thelarche), the pubertal growth spurt, and rapid bone age progression. Testosterone, on the other hand, causes penile enlargement, growth of pubic hair, and (following its conversion to estradiol) the male pubertal growth spurt. It is worth noting that isolated adult axillary odor, axillary hair, and pubic hair in boys and girls is associated with increased secretion of weak adrenal androgens, primarily dehydroepiandrosterone-sulfate (DHEA-S), in a process known as adrenarche (PA).

When evaluating a child who is undergoing early pubertal maturation, it is very important to differentiate between true precocious puberty and the common variants, such as PA and premature thelarche (PT). Premature thelarche results from transient secretion of small amounts of estradiol before the normal age of puberty. Thus, a girl with PT has isolated and non-progressive breast development without any other pubertal signs. Premature adrenarche, on the other hand, is caused by increased adrenal DHEA-S production before the normal age of puberty, leading to mild and slowly progressive androgen effects, such as adult body odor, axillary hair, and pubic hair. Thus, the presence of pubic/axillary hair in a girl who has no breast development or in a boy who has no testicular enlargement is likely to be PA. Findings suggesting pathological CPP include the presence of pubic hair and breast enlargement/testicular enlargement at the same time, advanced stages of pubertal development, increased linear growth, or advanced skeletal maturation.

The gold standard for diagnosing CPP is the GnRH stimulation test. Following the intravenous administration of GnRH, a peak stimulated LH $>$ 5 IU/L is indicative of CPP, although the exact cutoff used locally may vary depending on the particular assay used and its limit of sensitivity. A less commonly used criterion for girls is a ratio of peak LH/peak FSH $>$ 0.66 after GnRH stimulation. Another test that may prove helpful is measurement of the basal serum LH concentration using an ultrasensitive assay, which usually is $<$ 0.3 IU/L in prepubertal children. However, the ultrasensitive LH test is not typically available in hospital laboratories and must be interpreted with caution.

The cornerstone of CPP treatment in children with or without MMC is administration of long-acting GnRH analogs (GnRHa), with the main goal of preserving adult height. These analogs work by maintaining a constant level of GnRH activity that overrides the required pulsatility, resulting in suppression of LH and FSH secretion. There are many GnRHa in use around the world, each with different administration routes. For many years, the main agent in the U.S. was the leuprolide acetate depot intramuscular injection. Currently available leuprolide preparations are administered every 1–6 months. Other GnRHa used in the US include depot triptorelin, which is injected every 6 months, along with a subdermal implant containing histrelin that is surgically placed in the arm and changed every 1–2 years.

Patients with MMC have generally been excluded from clinical trials of GnRHa due to existing disturbances in growth and problems in achieving standardized measurements. Reports from the few studies of patients with MMC, hydrocephalus, and CPP treated

with the GnRHa triptorelin ($n = 5$) or leuprolide ($n = 3$) showed that elevated sex steroid levels and gonadotropins decreased during treatment. However, suppression to prepubertal levels was not achieved. Despite this, in all patients, menstruation and the progression of pubertal development ceased. The progression of bone age advancement slowed as well, but there was no appreciable change in height SDS and predicted adult height. There were no side effects noticed during this treatment [19].

Regular blood testing to monitor treatment efficacy remains controversial. Although some have advocated periodic ultrasensitive LH measurements or follow up GnRH stimulation testing while on therapy, it is unclear whether these add to the information provided by physical examination and bone age x-rays. Further, there is no evidence of any correlation between adult height and results of biochemical monitoring. In addition, there is uncertainty on the best time to discontinue GnRHa use. In general, it is better to individualize the approach based on the unique characteristics of each patient, including chronological age, actual and predicted height, pubertal maturation, psychosocial factors, and family preferences.

Current evidence indicates that GnRHa therapy is effective and safe. Children who have been treated with GnRHa for CPP have shown long-term outcomes that are promising in terms of body mass index, fertility, and bone mineral density. An important aspect of the treatment is to alleviate psychological distress from early puberty. Although inadequate, evidence suggests that GnRH treatment helps to reduce stress and decrease problematic behavior, especially in young girls for whom breast development and early menses are major concerns for both the caregiver and child [20,21]. Still, there are few data in the literature regarding the outcome of children with MMC and precocious puberty. Thus, further prospective research is required to investigate the impact of GnRH therapy in these children.

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The Spina Bifida Association has already embarked on a systematic process for reviewing and updating the guidelines. Future guidelines updates will be made available as they are completed.

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Conflict of interest

The authors have no conflicts of interest to report.

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