English Transcript

Interview with Dr. Brian Miyazaki

Dr. Eyal Ben-Isaac:

Hello and welcome to the Perspectives on Pediatrics podcast. I'm your host, Dr Eyal Ben-Isaac, recording from Children's Hospital Los Angeles. I have the pleasure of speaking with Dr. Brian Miyazaki, who's an attending physician in the Division of Endocrinology at Children's Hospital Los Angeles. Today we will be discussing the topics of precocious puberty and delayed puberty. Welcome Brian.

Dr. Brian Miyazaki:

Thank you. Thank you very much for having you today.

Dr. Eyal Ben-Isaac:

There are many terms that are used. Can we define some of the endocrinology terms, like adrenarche and gonadarche and so on, and what they mean?

Dr. Brian Miyazaki:

Sure, absolutely. I think when we discuss puberty, it's very important that we are familiar with the different terms used to describe puberty. To begin with, we have adrenarche and this indicates increased activity of the zona reticularis, which is the innermost layer of the adrenal cortex. Pubarche, thus, is the physical manifestation of adrenarche, where you have development of pubic hair, axillary hair, body odor and acne. Gonadarche reflects the reactivation of the hypothalamic gonadotropin

releasing hormone, or GnRH pulse generator. This then stimulates pulsatile gonadotropin secretion, which in turn stimulates growth and maturation of the gonads. Next there's thelarche, which is appearance of breast tissue, and then menarche is appearance of menstrual bleed.

Dr. Eyal Ben-Isaac:

Wonderful. What is the typical timing of puberty in girls and boys, and has that changed over the last several years?

Dr. Brian Miyazaki:

So within a few weeks of birth, there's a period of transient gonadotropin secretion, which were designated as mini puberty. But subsequently those signals go dormant until puberty, as we typically conceive of, occurs. In girls, this typically starts with thelarche, then progresses to pubarche,, and then menarche about two and a half years later. In boys, puberty presents itself as increased testicular volume, then increased penile length, and then pubarche. Prior to the 19th century, the average age of menarche was around 17 years and then in the late 20th century, this declined to about 13 years of age in Europe and North America. We have recent data in America through the cross-sectional Third National Health and Nutrition Examination Survey, or the NHANES III study, which showed that the average age of breast development for non-Hispanic black girls was nine and a half. For Mexican-American girls, was 9.8 years of age, and for non-Hispanic white girls, was 10.3 years of age. The average age of menarche was found to be 12.1 for non-Hispanic black girls, 12.2 for Mexican-American girls, and 12.7 for non-Hispanic

white girls. There are similar studies in North America and worldwide that have shown a trend of earlier onset of puberty, whereas the average age of menarche seems to be rather static.

Dr. Eyal Ben-Isaac:

Have we seen any changes in the boys' timing?

Dr. Brian Miyazaki:

Yes, though, the data is going to be a little bit less prevalent, just because a lot of studies are most related to girls.

Dr. Eyal Ben-Isaac:

So briefly, what are some of the important hormonal changes that lead to puberty? So we can understand, when we review the differential diagnosis in a little while, like, what is the reason for early and late puberty, and some of the causes that might be related to these hormonal changes.

Dr. Brian Miyazaki:

So the hormonal changes that lead to puberty are dependent on our hypothalamic pituitary gonadal, or HPG axis. After remaining dormant, GnRH begins to be secreted in a pulsatile fashion from the hypothalamus. GnRH then stimulates the pituitary gland to make luteinizing hormone or LH, and follicle stimulating hormone, or FSH. In males, LH stimulates the Leydig cells to produce testosterone, and FSH stimulates growth of the seminiferous tubules and supports sperm

development. In females, LH stimulates theca cells to make androstenedione, which then diffuses to the granulosa cell, where, with FSH, this stimulates estradiol production. Potential activators of GnRH secretion at puberty include kisspeptin and neuroplane B. Genetics accounts for the majority of the variability in the timing of pubertal onset in developed countries. Other factors may include overall health and the social environment that influence pubertal onset.

Dr. Eyal Ben-Isaac:

So what is the clinical definition we use now for early puberty?

Dr. Brian Miyazaki:

Early puberty is defined as pubertal onset that occurs below two and a half standard deviations below the mean. Hence, we traditionally define this to occur if secondary sexual characteristics occur before the age of eight in girls and nine in boys. This may vary depending on normative data in their regional practice.

Dr. Eyal Ben-Isaac:

Before we get into true precocious puberty, can we review some of the benign forms, such as premature thelarche.

Dr. Brian Miyazaki:

Yeah, premature thelarche refers to isolated breast development with normal linear growth velocity and without secondary sexual characteristics. Premature adrenarche refers to a mild form of androgen excess that usually manifests itself as

premature pubarche, in the sense of pubic hair development, axillary development, body odor and/or acne. In most situations, these are reassuringly benign findings. However, the timing of puberty, as we mentioned, in girls, that usually starts with breast development first, sometimes will start with pubarche. And so there is a chance that pubarche may lead to the development of true precocious puberty, and so clinical monitoring is still warranted.

Dr. Eyal Ben-Isaac:

What are some of the things that we should ask on the history or look for on exam to evaluate the signs of puberty?

Dr. Brian Miyazaki:

So for girls, Tanner staging can be used to communicate the degree of breast development. In stage two, there is an elevation of the breast and papilla that occur. This may also be unilaterally initially. In stage three, there is further development and enlargement of the breast and areola, but without separation and contour. During Tanner stage four, the papilla and areola form a secondary mound above the breast. And in Tanner stage five, this represents the mature breast development due to the recession of the areola to the contour of the breast. In boys, the onset of puberty is defined as testicular volume that's greater than four mLs and a testicular length that's greater than two and a half centimeters. And each Tanner stage represents further progression of the testicular volume and penile length. For staging of pubic hair, Tanner two is characterized by sparse growth of lightly pigmented hairs along the labia majora, or base of penis. When

hair becomes darker, coarser and spread to the pubic bones, we consider this. Tanner three. Tanner four corresponds to adult hair type, but goes to Tanner five when it starts to spread to the medial thigh. Another important aspect of assessing children with purplish puberty is utilizing the mid-parental target height. In boys, we calculate this by taking the father's height, adding it to the mother's height, adding five inches or 13 centimeters, and then dividing by two. So in essence, we make the mother into a boy by adding five inches or 13 centimeters and taking the averages of the two parents. For girls, we take the father's height, add it to the mother's height, and subtract five inches or 13 centimeters, and then divide by two. In terms of important history and exam findings, the old growth chart is a very crucial, important part of the evaluation. This will enable us to determine if there are concerns for accelerated growth velocity and possibly crossing of height percentiles. The timing of puberty in parents and siblings and heights of parents enables us to assess genetic factors. A review of symptoms such as headaches, abdominal pain, seizure activity and exogenous exposures to sex steroids or items with sex steroid like properties such as lavender or tea tree oils are also important components of the history. The physical exam would incorporate things like Tanner staging, assessment of midline defects, visual field abnormalities, a comprehensive thyroid exam and a skin exam.

Dr. Eyal Ben-Isaac:

Thank you for that great review. So let's say we think that maybe somebody has early puberty. Is there maybe any imaging or labs that we should think about

doing? Is the timing of the labs important? For example, doing morning versus afternoon versus evening labs.

Dr. Brian Miyazaki:

So if your history and physical suggest concerns for precocious puberty, your evaluation can begin with a bone age, and this is a radiograph of the left hand and wrist. This radiograph is then compared with an atlas of radiographs from children of known ages. This then can determine if there are concerns for either delayed or advanced bone ages. Further imaging, such as ultrasounds and MRI may be needed depending on the suspected etiology of precocious puberty. In terms of labs, we can obtain morning LH, FSH and estradiol or testosterone levels.The assay techniques that are used to measure these levels, preferably, if we use a third generation ICMA or a mass spec, will determine the reliability of results, because these assays will be better to detect the lower limit of detection. As these hormones are secreted in a pulsatile or diurnal pattern, the best time to capture this is early in the morning, when levels are at their peak. If the results are inconclusive, we can then perform what's called a GnRH agonist stimulation test that will further evaluate the HPG axis.

Dr. Eyal Ben-Isaac:

So let's try to go over the differential diagnosis. It appears an important part of the differentials to decide if this is coming from the brain, such as central or gonadotropin dependent puberty versus peripheral gonadotropin independent precocious puberty. Can you elaborate what that means?

Dr. Brian Miyazaki:

Yes, as you stated, the etiology of early maturation will help determine further evaluation and treatment options. So in cases of precocious puberty, you're going to have elevations of your sex steroids, either your estrogen or testosterone levels. But where is it coming from? In cases of central or gonadotropin dependent precocious puberty, you're going to have elevations of your gonadotropins, hence, your LH levels and your FSH levels are elevated along with your estrogen and testosterone levels. Whereas in peripheral or gonadotropin independent precocious puberty, your sex steroids, testosterone, estrogen are elevated, but this causes a negative feedback loop wherein your LH and FSH levels are then suppressed.

Dr. Eyal Ben-Isaac:

So what are some of the main causes of gonadotropin dependent precocious puberty that we should be aware of, and maybe how do we manage them?

Dr. Brian Miyazaki:

In cases of gonadotropin dependent precocious puberty or central precocious puberty, we want to examine for a central cause. One of the concerns for central precocious puberty is association of CNS lesions. Thus, an MRI of the brain may be a consideration for the workup, particularly in girls presenting much younger, such as below the age of six, and in all boys. If a child exhibits clinical signs of gelastic seizures, for instance, which are uncontrollable laughing spells, this would be a concern for the presence of hypothalamic hamartomas. Other less common CNS

lesions associated with central precocious puberty may include astrocytomas, ependymomas and pinealomas. Neurosurgical consultation would be warranted for appropriate management. Other causes may include irradiation, hydrocephalus, cysts, trauma or inflammatory disease. In cases of neurofibromatosis Type 1, central precocious puberty is typically due to optic gliomas. As we learn more about genes and genetic syndromes, we're gaining further understanding about the mechanism behind pubertal onset. For instance, MKRN3 and kisspeptin are important components of the GnRH pulse generator. We learned of their roles by identifying that mutations in their genes led to familial cases of central precocious puberty. And finally, untreated severe hypothyroidism has been associated with central precocious puberty. Though the exact mechanism is unclear, we hypothesize that there may be cross reactivity between TSH with the FSH receptor.

Dr. Eyal Ben-Isaac:

That's a great review. Now let's take it to gonadotropin independent precocious puberty, and what should we be aware of, and what to look for, and how do we manage?

Dr. Brian Miyazaki:

In cases of gonadotropin independent precocious puberty, we want to examine for peripheral causes. Thus, in your history, you may discover exogenous sources of sex steroids, such as a parent or grandparent that might be using topical forms of these medications. One of the most common causes in girls is a large functional ovarian follicular cyst. This often regresses on their own. Pelvic or testicular

ultrasounds would be helpful in detecting things like granulosa cell tumors, sertoli latex cell tumors, or gonadoblastoma. An hCG level would be useful in detecting hCG secreting tumors, which can be found in the gonad, brain, liver, retroperitoneum and posterior mediastinum. Androgen secreting tumors and congenital adrenal hyperplasia may be some adrenal etiologies of precocious puberty. Just as there are familial gene mutations which can contribute to central precocious puberty, inactivating mutation in the LH receptor has been shown to cause male familial GIPP or gonadotropin independent precocious puberty or otherwise known as testotoxicosis. This mutation can also occur in girls, but as girls rely both on the LH and FSH for ovarian steroidogenesis, the clinical presentation is less pronounced. And finally, there is McCune Albright syndrome, which is caused by a somatic mutation in the alpha subunit of G3 protein that activates adenylate cyclase. The classical triad includes gonadotropin independent precocious puberty, café-au-lait pigmentation that is irregular in shape and often does not cross the midline, and fibrous dysplasia of the bone. Thus, McCune Albright should be considered in girls with recurrent follicular cysts and cyclic menses, but with minimal breast development.

Dr. Eyal Ben-Isaac:

So management, of course, depends on the etiology. Hypothyroidism gets treated with synthroid, tumors may need to be resected and so on. But can you briefly review the use of GnRH agonists and why they are important?

Dr. Brian Miyazaki:

Sure, so GnRH agonist, keep in mind, will only be efficacious in cases of GDPP or central precocious puberty. Normally, the hypothalamus secretes GnRH, but in a pulsatile fashion. So yes, we did say treatment of GnRH agonist. And so this is the reason that in rare cases, there may be a side effect of causing a menstrual bleed in girls on initiation of treatment. However, as this treatment provides a sustained release, this then causes down regulation of the GnRH receptors in the pituitary gland. Hence, even though your hypothalamus is still secreting endogenous GnRH, you no longer have the receptors to respond to them, which then leads to down regulation of LH, FSH, and hence estradiol and testosterone levels. The decision to treat should be individualized, looking at height projections, looking at psychosocial readiness to handle menstruation.

Dr. Eyal Ben-Isaac:

This was a wonderful review of precocious puberty, a topic that is very hard to sometimes understand, but I think once you get down the hormones and the pathways and everything, it definitely makes a lot more sense. Now let's go over the other aspect, the other side, delayed puberty. What is the clinical definition of delayed puberty in males and females?

Dr. Brian Miyazaki:

Sure, delayed puberty we define it as absence or delayed onset of gonadarche at a chronological age that's greater than two standard deviations later than the population mean. So in girls, we define delayed puberty as absence of breast development by the age of 13, or lack of menarche by the age of 15. In boys, we

define this as a lack of testicular enlargement to a volume that's greater than four mLs by the age of 14.

Dr. Eyal Ben-Isaac:

What does stall puberty mean? And does that make you think of anything specific?

Dr. Brian Miyazaki:

So stalled puberty refers to a condition when there's initial progression of pubertal development that subsequently halts for a prolonged period. Usually it's more than a year without any further advancement of pubertal milestones, children with constitutional delay of growth in puberty or late blooming have delayed puberty rather than stalled puberty, when we consider etiologies. However, I think it's more important to think of the differential in terms of hypergonadotropic or hypogonadotropic hypogonadism/ So when there's gonado failure, the gonads fail to secrete their corresponding sex steroid, thus hypogonadism. Without the sex steroid, there's no negative feedback loop. This leads to increasing gonadotropins, and hence increasing LH, FSH secretion. On the other hand, hypogonadotropic hypogonadism refers to a central cause of pubertal delay. In this case, sex steroids are low and the LH and FSH may be low or inappropriately normal.

Dr. Eyal Ben-Isaac:

So that's a great way to break it down. So let's kind of go over maybe some of the causes of hypergonadotropic hypogonadism.

Dr. Brian Miyazaki:

Causes can be both acquired and congenital, so things like chemotherapy, radiation therapy, surgery, trauma, infections and autoimmunity are some examples of acquired etiologies. Galactosemia is a rare cause of delayed puberty. There are some sex chromosome abnormalities that can lead to gonadal failure. One cause is Turner Syndrome, which refers to deletions or structural rearrangements of the X chromosome. Presentation is quite variable, though short stature is invariably associated with Turner Syndrome. Girls with Turner Syndrome may have complete absence of puberty, stalled puberty, completion of puberty with infertility, and a very few may, in fact, have spontaneous pregnancy. Moving on to then Klinefelter syndrome, this is a chromosomal aneuploidy characterized by usually a 47 XXY karyotype. The onset of puberty is typically not delayed. However, men with Klinefelter Syndrome have incomplete puberty with firm testes on exam, Sertoli cell dysgenesis, variable testosterone dysfunction and impaired spermatogenesis.

Dr. Eyal Ben-Isaac:

Wonderful. So now let's switch it over. What are some of the main causes of hypogonadotropic hypogonadism.

Dr. Brian Miyazaki:

Similar to hypergonadotropic hypogonadism, causes of hypogonadotropic hypogonadism can be both acquired and congenital. Congenital causes may be associated with variants in genes involved in the development or migration of GnRH neurons, as well as genes involved in the secretion or action of GnRH. In embryogenic development, GnRH neurons develop in the olfactory placode. These

neurons then migrate with olfactory derived axons towards the cribriform plate. Thus, there may be an association between hypogonadotropic hypogonadism and decrease or lack of sense of smelling known as anosmia or hyposmia, and this is known as Kallman syndrome. There may be variation in genes such as PROP1 that can lead to impaired pituitary development. There's also a number of genetic syndromes related to hypogonadotropic hypogonadism, such as CHARGE Syndrome. Some acquired causes may be due to CNS tumors, such as craniopharyngioma or germ cell tumors, hyperprolactinemia due to prolactin secreting adenomas, trauma or infiltrative diseases affecting the infundibulum can also cause hypogonadotropic hypogonadism. And then another cause is often termed as functional hypogonadotropic hypogonadism. The root cause is a hypothalamic response to intense physical or emotional stress, caloric deficit or chronic systemic illness.

Dr. Eyal Ben-Isaac:

So earlier, we went over some of the important things we should be evaluating in the history and exam when assessing for precocious puberty, how about for delayed puberty?

Dr. Brian Miyazaki:

One of the important review system questions to determine is the sense of smell, as we discussed about earlier. There are congenital anomalies that are associated with syndromes that are associated with hypogonadism, whether there's micropenis, hearing loss, deafness, and then looking at a child's nutritional state,

looking at caloric intake, their BMI. An additional component that's important is the family history of pubertal onset. And in terms of physical exam Tanner staging to determine whether they are in puberty or have a stalled puberty type picture.

Dr. Eyal Ben-Isaac:

So now that we think maybe the child has some aspects of delayed puberty, is there any imaging or labs that we should do? Which ones?

Dr. Brian Miyazaki:

So similar to precocious puberty, we can start with a bone age, and this will determine if there is, in fact, a delayed bone age. Additional imaging may include an MRI that looks at the brain for any type of CNS process. In terms of labs, again, we can get the morning LH, FSH, estradiol and testosterone levels. Additionally, we may look at adrenal hormone levels such as DHEA sulfate, 17 hydroxyprogesterone, to rule out any type of adrenal causes. A prolactin level can be obtained to rule out hyperprolactinemia. And thyroid function tests should be done to rule out hypothyroidism as a reason for delayed puberty.

Dr. Eyal Ben-Isaac:

How do we manage pubertal delay?

Dr. Brian Miyazaki:

So we're starting to look at some novel treatments, such as GnRH therapy or kisspeptin therapy. But all in all, sex steroids still remain the mainstay of treatment.

In boys, traditional therapy uses intramuscular forms of testosterone esters enanthate or cyprionate There are subcutaneous regimens that are currently being utilized in studies. Gel formulations are available, though difficult to titrate at lower doses, and there's also concerns for household exposure. In girls, transdermal estradiol is often used for pubertal induction. Oral formulations such as ethanol estradiol or conjugated equine estrogens can also be used, though most combined oral contraceptives should be avoided due to the relatively higher estrogen doses in these formulations. Around 18 to 24 months later, progesterones are added to induce withdrawal bleeding to minimize the risk of endometrial hyperplasia.

Dr. Eyal Ben-Isaac:

So since the majority of cases are due to constitutional delay of puberty, can we spend some time talking about what that means?

Dr. Brian Miyazaki:

So constitutional delay of growth in puberty is the most common cause of delayed puberty. Accounts for about half or above half of the cases. Most of these are going to be male in origin, and it's due to a transient functional defect in the production of GnRH from the hypothalamus. This is caused by individual genetic variations in the ensemble of hypothalamic and pituitary genes controlling sexual maturation. Constitutional delay tends to have a familial pattern of inheritance, often following an autosomal dominant pattern, such that multiple family members from multiple generations often have a history of late blooming. One option is what we call watchful waiting with reassurance and psychological support for the patient and

family. However, in certain situations, we may consider short term hormonal therapy with testosterone in males and estradiol in females. One example is to use testosterone and enanthate or cypionate at a dose of 50 milligrams IM once monthly for six months, and then reassess for endogenous gonadal function and size six months later. In many patients, this therapy is associated with pubertal development indicated by testicular enlargement and increasing testosterone concentrations after cessation of therapy. This then will rule out any concerns for isolated GnRH agonist deficiency once a child gets into puberty.

Dr. Eyal Ben-Isaac:

Brian, that was an incredible, wonderful review of both precocious and delayed puberty, which really have both physical and mental implications on the child and the family. So thank you so much for that great review.

Dr. Brian Miyazaki:

Absolutely.