Panel Discussion

“Gonadal Suppression Therapy: Pros and Cons”

Gonadal Suppression Therapy

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Gonadal suppression therapy, originally a therapy for central precocious puberty (Fig. 1), is often actually applied to treatment of short stature in clinical practice. The premature secondary sexual characteristics of present-day Japanese are defined as follows:

Boys:

- (1) Growth of penis, scrotum and testes at age under 9.
- (2) Appearance of pubic hair at age under 10.
- (3) Appearance of axillary hair/beard or voice breaking at age under 11.

Girls:

- (1) Breast development at age under 7.5.
- (2) Appearance of pubic hair/axillary hair at age under 8.
- (3) Genital bleeding at age under 9.

However, due caution is required for cases meeting the criteria at an age one year higher than the ages specified above; and a rule is followed that the above criteria are applied to children with -1 SD or less of height on the basis of ages one year higher than the ages specified because their adult heights would become short.

In the case of Fig. 2, a girl showed breast development at an age of two. We started treatment with cyproterone acetate because her secondary sexual characteristics continued to advance. However, she had her menarche at the

age of four in spite of the above therapy, so we changed the medicine to Leuplin[®] which was under clinical trial at that time. As a result, promotion of height growth and skeletal maturation were inhibited and she finally attained a height of more than 160 cm.

Thus typical precocious puberty cases developing second sexual characteristics aged three to four are mostly treated without hesitation with the aim of improving their social adaptation. Here some questions of relevance are: Will all patients with precocious puberty result in short stature if they are not provided with treatment? Will short stature be improved if the patients are treated? What should we do in a case that is affected by precocious puberty at a borderline age around six? Must she (or he) be treated?

In sporadic precocious puberty, the lower the onset age, the earlier the growth in height ends,

Fig. 1 Central precocious puberty.

Fig. 2 Growth curve of a girl with classical precocious puberty

Fig. 3 Growth curve of a girl with slowly progressive precocious puberty

resulting in shorter adult height. However, such patients grow at a higher pace than normal children during the spurt and thus are not likely to have an extremely short adult height.

In addition to classical precocious puberty, there is a type called “slowly progressive type” precocious puberty, which develops slowly. It is reported that patients with this type of precocious puberty will not have an extremely short height even if they do not receive treatment. In my experience, while cases that enter puberty at early ages such as from one to three, mostly develop symptoms of precocious puberty rapidly, many of the cases that show precocious secondary sexual characteristics at ages from five to seven are merely extremely early in physiological development rather than exhibiting precocious puberty. In addition, even a case diagnosed as precocious puberty will not result in an extremely short final height if the individual already has a certain degree of height.

Cases with a slowly progressive type or a transient type slowly develop symptoms of

precocious puberty and tend to reach a fairly tall height.

We followed up the case of Fig. 3 every three months without providing the patient with treatment, this was due to the following reasons: she was likely to reach a adult height of more than 150 cm without treatment (with her skeletal age not having advanced too much for her height age), and she was sound in mind. She is now 10 years old and is 155 cm tall. Accordingly, she seems to have suffered from a slowly progressive type precocious puberty. However, if she has menarche in the near future, the appearance is considerably precocious. In that case, if she cannot stand the precocious puberty mentally, we mean to provide her with treatment to improve her social adaptation.

We followed up the next case (Fig. 4) without providing the patient with treatment because she was likely to reach more than 150 cm without treatment because she was 140 cm tall at the age of nine. After that, as the child patient had menarche and complained of slight mental instability, we provided her with gonadal suppression only for a

Fig. 4 Growth curve of a girl with borderline precocious puberty

short term with the aim of adjusting the time of menarche to her classmates. Although the growth of height significantly slowed during the treatment, she fortunately started to gain height

Fig. 5 Adult height of female children with precocious puberty with/without LHRHa therapy

after the cessation of the treatment and she is over 160 cm at present. Thus, the gonadal suppression therapy provided in this case was intended to improve the social adaptation of the patient and not intended to increase adult height.

One of the important points to keep in mind in relation to gonadal suppression therapy using a gonadotropin releasing hormone analog (LHRHa) is that the growth rate may slow down extremely,

Fig. 6 Adult height of untreated female children with precocious puberty

Fig. 7 Adult height of female children with precocious puberty who with/ without LHRHa therapy

especially when the skeletal age has advanced. Because complete inhibition of sex hormones is likely to retard height growth, it is considered advisable to provide treatment with the minimum dose of LHRHa sufficient to suppress gonadal functions.

According to domestic and overseas reports relating to therapy for girls with precocious puberty using LHRHa, while the predicted height after completion of treatment considerably improved from the predicted height before initiation of treatment and neared the target height, discontinuation of the treatment resulted in rapid advancement in skeletal age and an adult height shorter than the predicted height in many cases. Figure 5 is a comparison of use or non-use of LHRHa therapy. Many reports indicate that the adult height exceeded the target height in treated cases, whereas it did not exceed the target height in untreated cases. Thus, treatment is considered worth trying. However, in terms of comparison at the onset age of precocious puberty, while adult height significantly fell short of the target height in

cases that were affected by precocious puberty at an age of six or younger and were untreated, the adult height did not differ much in cases that were affected by precocious puberty at ages older than six years. In addition, the adult height of untreated patients fell significantly short of the target height in the typical rapidly progressive type of precocious puberty; whereas, the differences between actual adult heights and target heights were very slight in the slowly progressive type (Fig. 6). Furthermore, adult heights were significantly improved by treatment in cases that were affected by precocious puberty at an age of six or younger as shown in Fig. 7, but adult heights did not differ much irrespective of whether treated or untreated in cases that were affected by precocious puberty at an age older than six years. Also, it is considered that the therapeutic effects of LHRHa are not so high in early puberty where puberty conditions are normal, but adult height is likely to be short due to short stature at the onset of puberty (precocious for the height).

My own conclusions drawn from the above findings are as follows:

- 1) Treatment is required for improvement of psychosocial adaptation in cases with young onset age of precocious puberty.
- 2) In cases with a high onset age of precocious puberty, treatment for a child patient who is

sound in mind is intended only to improve adult height; however the improvement in adult height is not very promising in such cases. Nevertheless, the treatment will be certainly needed in cases where psychosocial adaptation needs to be improved.