

**Research paper****Precocious pseudopuberty due to autonomous ovarian cysts: A report of ten cases and long-term follow-up**

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*Vestische Kinder, Jugendklinik Datteln, University of Witten/Herdecke, Datteln, Germany***ABSTRACT**

**We report the findings and clinical course of ten girls aged 0.2 to 6.3 years with precocious pseudopuberty due to autonomous ovarian cysts. We found elevated oestrogen levels in five patients and failure of gonadotropin response to GnRH stimulation in four patients during the first episode, of the disease. In one patient, a GnRH stimulation test was not performed. Pelvic ultrasound examination showed large ovarian cysts in all ten patients. Following the initial episode the secondary sexual characteristics of nine patients regressed completely without treatment. The cyst of one girl was removed surgically on demand of her parents. Three girls presented recurrent autonomous ovarian cysts. Two of these girls developed central precocious puberty requiring treatment with a GnRH-agonist after repeated episodes of precocious pseudopuberty. We started treating the third girl with a GnRH agonist after the second relapse of the autonomous ovarian cyst because of rapidly advancing bone age. We conclude that in the majority of cases autonomous ovarian cysts regress spontaneously and that surgery is in general not indicated. Furthermore, autonomous ovarian cysts can relapse before the onset of physiological puberty and accelerate biological maturation leading to central precocious puberty and consequent decrease of height potential.**

**Key words:** Autonomous ovarian cysts , Central precocious puberty, GnRH agonist, Precocious pseudopuberty

**INTRODUCTION**

Autonomous ovarian cysts are rare in prepubertal girls. Millar et al reported that ovarian cysts are found in prepubertal girls with a frequency of 2% to 5%.<sup>1</sup> Autonomous ovarian cysts were present in 5%

of the girls with ovarian cysts.<sup>1</sup> Autonomous ovarian cysts can cause isosexual precocious pseudopuberty.<sup>2</sup> Differentiating central precocious puberty from precocious pseudopuberty, e.g. due to autonomous ovarian cysts, is very important, as the management of these two clinically similar conditions is different. While treatment of central precocious puberty usually requires a GnRH agonist, in general no treatment is necessary for precocious pseudopuberty due to autonomous ovarian cysts.

We report ten girls who presented with signs of

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*Received 23-05-07, Revised 20-10-07, Accepted 10-02-08*

sexual precocity due to autonomous ovarian cysts.

## PATIENTS

In Table 1 the clinical characteristics, laboratory findings, and the results of imaging studies at the first episode of precocious pseudopuberty are presented. After the first episode of the disease, the secondary sexual characteristics of nine girls regressed completely without treatment along with a complete regression of the ovarian cysts noted by sonography. One girl underwent unilateral ovariectomy on demand of her parents. In all patients  $\alpha$ -1-fetoprotein and  $\beta$ -human chorionic gonadotropin were within the normal range. Three girls presented recurrent autonomous ovarian cysts (Table 2) and are described below in more detail.

Patient No. 2 presented three episodes of precocious pseudopuberty at the age of 6, 7, and 7.7 years. On the 3rd recurrence, besides breast development, swelling of the labia minora, and vaginal discharge, pubic and axillary hair were also noticed. Thus, on this occasion the pubertal stage was B<sub>3</sub>PH<sub>2</sub> according to Tanner and Whitehouse.<sup>3</sup> The growth velocity was 15 cm/year and her bone age was advanced by 3 years. Prospective height potential was diminished by 8 cm. Laboratory examinations showed elevated oestrogen levels and an ovarian cyst was detected in the left ovary by ultrasound (4.5 cm in diameter). We treated the girl with a GnRH agonist for 3 years and 8 months until the age of 11 years in order to prevent a further loss of height potential. The total gain in height was 6 cm. During GnRH agonist treatment, the growth velocity was between 2 and 4 cm/year and there was no

**Table 1.** Clinical data, bone age, ultrasound findings, and laboratory findings of ten girls with autonomous ovarian cysts at the first episode of sexual precocity.

No.	History and clinical findings	Chronological age (years)	Bone age (years)*	Pubertal stage**	Largest diameter of cyst in ultrasound	Oestradiol (pg/ml) normal <20.0	Oestron (pg/ml) normal <20.0	LH/FSH after GnRH
1	Thelarche, vaginal discharge	4.5	4.5	B <sub>2</sub> PH <sub>1</sub>	3.8 cm	7.0	<20.0	prepubertal response
2	Thelarche, enlargement of labia minora, vaginal discharge	5.3	5.0	B <sub>2</sub> PH <sub>1</sub>	4.0 cm	59.0	43.0	suppressed
3	Thelarche, enlargement of labia minora, vaginal discharge	4.8	5.0	B <sub>2</sub> PH <sub>1</sub>	3.2 cm	<5.0	<20.0	prepubertal response
4	Vaginal bleeding	0.2	-	B <sub>1</sub> PH <sub>1</sub>	3.2 cm	250.0	-	-
5	Thelarche, enlargement of labia minora, vaginal discharge	4.7	5.0	B <sub>2</sub> PH <sub>1</sub>	6.0 cm	172.0	96.0	suppressed
6	Thelarche, vaginal bleeding	6.3	6.0	B <sub>2</sub> PH <sub>1</sub>	3.0 cm	242.0	-	suppressed
7	Thelarche	5.0	5.5	B <sub>3</sub> PH <sub>1</sub>	3.5 cm	<5.0	<20.0	prepubertal response
8	Thelarche	6.0	6.5	B <sub>2</sub> PH <sub>1</sub>	3.5 cm	<5.0	<20.0	prepubertal response
9	Thelarche, vaginal discharge	5.6	5.0	B <sub>2</sub> PH <sub>1</sub>	4.0 cm	<5.0	<20.0	prepubertal response
10	Thelarche, vaginal bleeding	4.7	6.5	B <sub>2</sub> PH <sub>1</sub>	3.5 cm	310.0	-	suppressed
	Mean value and standard deviation	4.7 ± 1.8	5.6 ± 0.7	-	3.8 ± 0.9	-	-	-

\* According to Greulich and Pyle<sup>13</sup>; \*\* according to Tanner and Whitehouse<sup>3</sup>

**Table 2.** Number of episodes and treatment of ten girls with autonomous ovarian cysts.

No.	Number of episodes	Treatment
1	1	none
2	5	initially none. GnRH agonist for 3 years after onset of central precocious puberty
3	1	none
4	1	none
5	1	unilateral ovariectomy on demand of parents
6	3	initially none. GnRH agonist after the onset of central precocious puberty
7	1	none
8	1	none
9	1	none
10	3	initially none. GnRH agonist after the second relapse because of advancing bone age

further advancement of the bone age and no further development of the secondary sexual characteristics. The bone age was appropriate for chronological age at the end of treatment. However, we must mention that two further relapses of the autonomous ovarian cyst occurred during the period of treatment.

Patient No. 6 experienced an episode of precocious pseudopuberty due to an autonomous ovarian cyst at the age of 6.3 years. After the first relapse of the ovarian cyst, breast development continued for a year although the cyst had regressed spontaneously. We considered this progression of breast development as a consequence of the maturation of the GnRH pulse generator due to repeated exposure to oestrogen. At the age of 8 years, her growth velocity was 8.4 cm/year and her bone age was advanced by 2 years with a decrease of height potential. Because of this evolution we began treating the girl with a GnRH agonist at the age of 9 years. Up to now, aged 10.5 years the child has experienced one further relapse of the ovarian cyst while on treatment with a GnRH agonist.

Patient No. 10 experienced her first episode of precocious pseudopuberty due to an autonomous ovarian cyst at the age of 4.7 years. At this time, bone age was advanced by 1.8 years. Four months later, the girl experienced the first relapse of the autonomous

ovarian cyst. At the age of 5.1 years, a second relapse of the autonomous ovarian cyst was observed. The girl showed no skin lesions characteristic of McCune-Albright syndrome. We performed a radionuclide bone scan, which did not reveal any abnormalities. After the second relapse of the autonomous ovarian cyst, the bone age of the girl was advanced by 3 years. Because of the rapidly advancing bone age, we started treating the girl with a GnRH agonist at the age of 5.2 years. Up to now, aged 5.7 years, the patient has experienced no further relapse of the ovarian cyst during the ongoing treatment.

Four of the present patients were reported in 1991 by Andler in the German literature<sup>4</sup> (patients 1, 2, 3 and 5). They were included in this publication along with the available follow-up information for completion. Andler's description refers to the initial episode.

## DISCUSSION

The diagnosis of precocious pseudopuberty due to autonomous ovarian cysts is based on the history, clinical presentation, laboratory findings, and imaging, mainly by ultrasound. Girls with precocious pseudopuberty due to autonomous ovarian cysts present with signs of oestrogenisation, such as rapid bilateral breast development, vaginal discharge or bleeding, and swelling of the labia minora. The usual laboratory findings are elevated oestrogen levels with a suppressed gonadotropin response after GnRH-stimulation. In most cases, bone age is not advanced. Pelvic ultrasound examination can demonstrate unilateral or bilateral ovarian cysts (Figure 1). These findings, however, depend on the stage of the disease. Autonomous ovarian cysts develop and regress spontaneously at the latest after 2 to 3 months, while the clinical signs of sexual precocity may still be present after hormone levels are normalised and the ovarian cyst is not detectable by ultrasound.

Rodriguez-Macias et al reported that the diameter of the ovarian cyst, measured by sonography, at the initial episode is of great importance, as a diameter  $\geq 9$  mm is a strong indicator of autonomous ovarian activation.<sup>5</sup> Millar et al came to a similar conclusion and reported that ovarian cysts associated with precocious pseudopuberty are generally larger than 2



**Figure 1.** Autonomous ovarian cyst (Blase=urinary bladder; Zyste=cyst).

cm in diameter, whereas small cysts (less than 1 cm in diameter) are clinically insignificant.<sup>1</sup> Fakhry et al examined three girls with precocious pseudopuberty due to autonomous ovarian cysts. The cysts of these girls were between 2.2 and 5.5 cm in diameter.<sup>6</sup> The diameter of the ovarian cysts in our patients ranged from 3 to 6 cm.

Girls with signs of sexual precocity require a careful diagnostic work-up. The differential diagnosis of female sexual precocity includes conditions such as premature thelarche, premature menarche, central precocious puberty, and precocious pseudopuberty.<sup>7</sup> As reported by Mitrovic et al, an etiologic diagnosis can frequently be made on the basis of clinical signs, bone age assessment, oestradiol levels, GnRH-stimulation testing, and pelvic ultrasound examination.<sup>7</sup> In girls presenting with precocious pseudopuberty, the granulosa-cell tumour is a very important differential diagnosis to be considered, as 70% of all girls with granulosa-cell tumours develop precocious pseudopuberty.<sup>8</sup> The laboratory findings can be similar, as 85% of the patients with this tumour show elevated oestrogen levels with suppression of gonadotropin secretion.<sup>8</sup>

Recurrent autonomous ovarian cysts can also be a symptom of the McCune-Albright syndrome,<sup>2</sup> which in its classic form consists of at least 2 features of the triad: polyostotic fibrous dysplasia, café au lait skin pigmentation, and autonomous endocrine hyperfunction. Gonadal hyperfunction is the most frequent en-

docrine dysfunction in females with McCune-Albright syndrome (MAS), and precocious pseudopuberty is usually the first manifestation of MAS in children.<sup>9</sup> The MAS is the result of a postzygotic somatic mutation in the gene coding the alpha subunit of the stimulatory G protein (Gsa). Patients No. 2, No. 6, and No. 10 experienced recurrent autonomous ovarian cysts. We did not observe skin lesions characteristic of the MAS in these three patients. A radionuclide bone scan to detect or rule out polyostotic fibrous dysplasia was performed in Patient No. 10 and revealed no abnormalities. A radionuclide bone scan would have been of interest in Patient No. 2 and Patient No. 6, as well, but was not performed. However, during follow-up examinations there was no clinical evidence of bone involvement such as gait anomalies (including limp), visible bony deformities, bone pain or joint stiffness. Furthermore, no other endocrinopathies associated with MAS were seen, such as goiter, diabetes mellitus, acromegaly or Cushing syndrome. However, a form frauste of MAS cannot be excluded in our patients. As clinical evidence for MAS can appear later in the course of recurrent autonomous cysts,<sup>5</sup> a careful clinical observation of patients with recurrent autonomous ovarian cysts and/or molecular studies may be necessary in such cases.

As autonomous ovarian cysts represent a self-limiting disorder, no treatment is necessary. The spontaneous regression of the cysts is followed by the regression of almost all pubertal signs and the normalisation of the hormone levels. Surgery is therefore only indicated in the rare case of ovarian torsion, or if development of the secondary sexual characteristics and the ovarian cyst persist more than 3 months. The data on the clinical course of our patients therefore, confirms the opinion of other authors that girls with autonomous ovarian cysts, in general, require a conservative approach.<sup>5,10,11</sup> However, relapses of autonomous ovarian cysts with recurrent episodes of precocious pseudopuberty may lead to a prolonged or repeated exposure to oestrogen and can therefore result in a maturation of the GnRH pulse generator. Such an evolution from precocious pseudopuberty to central precocious puberty is called “combined precocious puberty”, an evolution which may require GnRH therapy.<sup>12</sup> As expected, and also shown by present data, GnRH treatment does not prevent

ovarian cyst recurrence.

## IN CONCLUSION

Autonomous ovarian cysts represent a rare, self-limiting endocrine disorder in prepubertal girls. In general, surgery is not indicated for their treatment. Therapy with a GnRH agonist, however, may become necessary in the case of transformation from precocious pseudopuberty to central precocious puberty after recurrences of the ovarian cysts. In such cases, a further loss of height potential can be prevented by treatment with a GnRH agonist, but further relapses of the autonomous ovarian cyst cannot be prevented by such intervention.

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