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Original Research Article

Polycystic ovarian syndrome in adolescence - significance of clinical and ultrasound criteria as per Rotterdam consensus

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Abstract: Polycystic ovarian syndrome (PCOS) in adolescents remains a diagnostic dilemma to the clinician. Many physiological changes occur in adolescents during the transition to an adult, including irregular periods, acne and weight gain, which along with mild enlargement of ovaries during puberty add to the confusion during ultrasonography. Our study aims at estimating the proportion of menstrual irregularity, clinical hyperandrogenism and polycystic ovaries on ultrasound scan (USS) in adolescent girls diagnosed to have polycystic ovarian syndrome by Rotterdam criteria. The study also aims to assess the significance of each variable in diagnosing PCOS. The study population included 144 adolescent girls between 15 - 19 years of age, diagnosed to have PCOS by Rotterdam criteria. They underwent USS evaluation for presence of polycystic ovaries. The results of clinical evidence of hyperandrogenism, hirsuitism assessment by Ferriman–Gallwey score and BMI were collected. The relation of these parameters was compared with ultrasound findings. The prevalence of PCO in PCOS in the present study was 82.63%. Menstrual irregularity was the commonest symptom and had strong association with USS diagnosis of PCO. There was significant association of clinical hyperandrogenism and hirsuitism with presence of PCO on ultrasound. PCOS is a disease which is difficult to diagnose, especially in the adolescent age. However, identification of PCOS and early institution of treatment can prevent systemic complications to a large extent. Diagnosing PCO on USS has a significant role in making a confident diagnosis of PCOS in adolescents.
Keywords: Polycystic ovarian syndrome (PCOS**),** adolescent.

INTRODUCTION

The combination of oligomenorrhoea, infertility, hirsuitism and bilateral enlarged polycystic ovaries was identified as an entity by Stein and Leventhal (1935), who for some time gave their name to the syndrome. The term ‘polycystic ovary syndrome’ and its acronym PCOS appeared in the 1960s and gradually replaced the Stein–Leventhal syndrome designation [1]. Polycystic ovary syndrome (PCOS) is the commonest endocrine disorder in women characterised by chronic anovulation, hyperandrogenism (clinical or biochemical), polycystic ovaries and typically presents during adolescence. The clinical and biochemical presentation is heterogeneous, but elevated serum concentrations of androgens are the most consistent biochemical abnormality and may be considered to be the hallmark of the syndrome. Many women with PCOS also have insulin resistance and hyperinsulinaemia, which may contribute to the clinical and endocrine abnormalities [2]. The etiology of this heterogeneous condition remains obscure, and its phenotype expression varies which makes the clinical care and research challenging [3].

The nosological difficulties presented by PCOS are not new. They were most poetically characterized by Netter *et al.;* who stated in 1958 that

"the syndrome of Stein (as PCOS was previously known) is a fugitive syndrome, with limits less well defined than those of the Sahara or the Sudan." [4, 5]. The first attempt to develop a standard diagnostic criteria for PCOS came 55 years after its initial description . The NIH criteria, formulated at a conference sponsored by NICHD (National Institute of Child Health and Human Disease of the United States) in 1990. It included the metabolic and reproductive aspects of the syndrome and was effectively used as a research tool. The main controversy was that it didn't include the polycystic ovarian morphology (PCOM) as a criterion. Consequently, another expert conference was held in Rotterdam in 2003, sponsored in part by the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM), recommending inclusion of PCOM in the criteria. Rotterdam criteria are widely followed both in research and practice. In 2006, an expert panel of the Androgen Excess Society recommended a modification of the Rotterdam criteria to require hyperandrogenism as an essential diagnostic criterion. All criteria require exclusion of other disorders: hyperprolactinemia, nonclassic congenital adrenal 21-hydroxylase deficiency, thyroid dysfunction, androgen-secreting neoplasms, and Cushing's syndrome [5].

Criteria for the diagnosis of Polycystic Ovary syndrome (Other hormonal or androgen excess conditions being previously excluded)

NIH / NICHD 1990	**ESHRE /ARSM (Rotterdam criteria) 2004**	**Androgen Excess Society 2006**
All of the following	Two of the following	All of the following
Clinical and / or biochemical hyperandrogenism	Clinical and / or biochemical hyperandrogenism	Clinical and / or biochemical hyperandrogenism
Menstrual dysfunction	Oligo ovulation or anovulation Polycystic ovaries	Ovarian dysfunction and / or polycystic ovaries

Abbreviations: ESHRE/ASRM = European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine; NIH/NICH = National Institutes of Health/National Institute of Child Health and Human Disease. Adapted from Clin Epidemiol. 2014; 6:1-13**.**

The past decade of research into PCOS has produced important new insights into the evaluation and treatment of this disorder. However, the diagnosis of polycystic ovarian syndrome in adolescents is still a challenging task [6]. Menstrual irregularity is common during the early years after menarche and oligo-anovulation may be normal. Clinical hyperandrogenism (HA) may be less common in younger women. Biochemical HA is the most consistent biochemical abnormality in PCOS but there are no widely accepted normal values for adolescence. Ovarian appearance in the early post-menarchal years may differ from that seen in adult women. Further, assessment of ovarian morphology is limited due to the transabdominal approach used in girls who are not sexually active. Hence, clinicians are faced with young women showing potential features of PCOS, with little guidance on how these features can be discriminated from the normal developmental process.[7] These considerations have led to the suggestion that all three elements of the Rotterdam criteria should be present in teenagers to make the diagnosis of PCOS [8].

Three consensuses (the ESHRE/ ASRM-Sponsored PCOS Consensus Workshop Group) on the various aspects of PCOS have taken place [3]. The first one in Rotterdam, Netherlands, in 2003 focused on diagnostic criteria for PCOS. The second in Thessaloniki, Greece, in 2007 dealt with infertility management in PCOS. The third in Amsterdam, Netherlands, in 2010, attempted to summarize current knowledge and to identify gaps in knowledge regarding various women's health aspects of PCOS.

The Amsterdam workshop has formulated important conclusions regarding adolescent PCOS:

1. Criteria for the diagnosis of PCOS in adolescents differ from those used for older women of reproductive age
2. Groups at risk (e.g., obese, hirsute, irregular menses) should be identified, but physicians should be cautious of overdiagnosing PCOS.

3. Individual PCOS manifestations in adolescents (e.g., obesity, hirsuitism, and irregular menses) should be treated.
4. There is an increased risk for infertility, dysfunctional uterine bleeding, endometrial cancer, obesity, type II diabetes, dyslipidaemia, hypertension and possibly cardiovascular disease, especially when PCOS is identified in early years of life. So early diagnosis and treatment is necessary to improve long term health [7].

The polycystic ovarian morphology was defined as the presence of 12 or more follicles, measuring between 2 and 9 mm, throughout the entire ovary and / or an ovarian volume >10 cm^3 (The Rotterdam ESHRE/ASRM sponsored PCOS Consensus Workshop Group, 2004) [9]. Since their initial proposal in 2003, an increasing number of reports have appeared questioning the utility of polycystic ovaries to serve as a marker of PCOS. The recent AACE/ACE Disease State Clinical Review [6] mentions the New AES guidelines, which are based upon a review of the data published using new ultrasound technology. When using the new ultrasound machines, diagnosis of PCOM is possible in patients having at least 25 small follicles (2 to 9 mm) in the whole ovary. The ovarian size threshold has not been influenced by new technologies, and 10 ml remains the threshold between normal and increased ovary size [1]. However, the authors recommend application of this threshold with use of newer imaging technology (essentially transducer frequency ≥8 MHz) among population aged 18–35 years. Wide literature search could not yield any reports establishing the role of the newer criteria in adolescent population. Many similar studies have used the adult criteria in adolescents as well (Nidhi et al) [10]. The present study uses the broader Rotterdam criteria, because of its wide acceptance and the lack of other established criteria for selecting adolescents with PCOS.

Despite PCOS being considered the most common endocrine disorder in women of reproductive age, the prevalence estimates are highly variable, ranging from 2.2% to as high as 26% [11]. A retrospective birth cohort study [10] to estimate the prevalence of PCOS, using all the three criteria, found prevalence of 8.7 +/- 2.0% (using NIH criteria), 17.8+/- 2.8% (using Rotterdam criteria) and 12.4 +/- 2.4 % (using AES criteria). These studies included women in 18-45 years age and showed that the prevalence rates of PCOS depend to a great extent on the criteria used to define this disorder. The data regarding prevalence of adolescent PCOS is even lesser. A cross-sectional community-based study from Mumbai reported a prevalence of PCOS among young women (15-24yrs) of 22.5% by Rotterdam and 10.7% by Androgen Excess Society criteria. The prevalence of adolescent PCOS in Nellore district was 15.4% [12] in the age range 10-19 years, whereas the prevalence was 3.7 % in a study from Lucknow (women 18-25 years) [13]. The study by Nidhi *et al.;* from Andhra Pradesh reported a prevalence of PCOS of 9.13 in Indian adolescents (15-18 years).[10] Other Asian populations studies have reported lower prevalence rates: 6.3% in Sri Lankan population and 2.4% in Chinese population. They attribute this higher prevalence in India to the strong etiological link between PCOS and diabetes, as India has higher prevalence of diabetes, compared to other Asian countries (Nidhi et al) [10].

MATERIALS AND METHODS:

Study design: Prospective cohort study.

Study duration: 15 months

Study population: Girls between 15-19 years of age were selected through Anganwadi based adolescent reproductive health camps, in Thiruvananthapuram district.

Methodology:

The study was conducted in the adolescent clinic of CDC. The girls were called in batches to CDC accompanied by their parents**,** by prior appointment and underwent physical examination, anthropometric measurements and ultrasound, in one visit. A detailed informed consent was taken for the participation in the study and from parents, if less than 18 years. The details entered in the standard questionnaire, and results of physical and anthropometric examinations and relevant investigations were recorded in the proforma. All the girls underwent transabdominal ultrasound using VIVID S5 (GE health Care systems) and 3-5 MHz transducer (Transvaginal ultrasound was not done as all girls were unmarried) and findings recorded.

Since it was a community based programme, the girls were called in randomly for USS and all were not in their follicular phase of menstrual cycle, at the time of USS, contrary to what highlighted in previous studies [2]. Examination was repeated for those who are not in the preovulatory phase, just after their next periods. Those ovaries

with follicles >10mm in size / with cysts also underwent repeat USS in the next cycle. Trans abdominal USS was done after adequate filling of the urinary bladder. Ovarian volume was calculated by taking maximum longitudinal (length) and maximum transverse measurements (width and depth). Ovarian volume was determined using the simplified formula for an ovoid (0.5×length×breadth×height). The counting of follicles was done similarly by sweeping the USS beam along the longitudinal as well transverse planes, taking care not to recount any follicle [14]. Even with full bladder, 4 ovaries could not be evaluated properly, in four girls. Hence, four girls were included with details of one ovary only. Non visualisation of ovary by transabdominal USS is well-known, cause being high location in the abdomen, increased parietal fat and excessive bowel gas. The USS examination was done by the same Radiologist for all the study subjects, who was blinded to the results of other two criteria.

Definition of Variables:

Menstrual Dysfunction: Chronic anovulation, generally presenting with oligomenorrhoea or secondary amenorrhea, is one of the key elements for the diagnosis of PCOS in the adult [8]. If cycle length is >35 days, it may be assumed that chronic anovulation is present and no special tests are needed. During adolescence, a cycle length up to 40 days may be considered normal, with longer menstrual cycles indicating oligomenorrhea.[6] It has been suggested that oligomenorrhoea persisting 2 years after menarche should be used as a criterion for the diagnosis of PCOS in adolescents, when combined with other two criteria [8].

Clinical Hyperandrogenism: Clinical Hyperandrogenism was assessed as the degree of hirsuitism using the Hatch modification of Ferriman-Gallway (mFG) scoring method [14-16].

Polycystic ovaries: One of the following two criteria has to be met for the diagnosis of polycystic ovary: either 12 or more follicles measuring 2–9 mm in diameter or increased ovarian volume (>10 cm3). The presence of a single polycystic ovary is sufficient to provide the diagnosis [17, 18].

BMI: Measured as weight in kg divided by height in meter^2, classification based on modified ELIZ chart for adolescents [14].

RESULTS

144 adolescent girls diagnosed to have polycystic ovarian syndrome by Rotterdam criteria were evaluated in this study. A positive family history of PCOS, especially in the mother, was present in 12.5% of the girls. Among them, 141 (97.91%) presented with menstrual irregularity, and 118 (81.94%) with clinical features of hyperandrogenism. The ultrasound scan could identify 119 (82.63%) girls with polycystic ovaries as per the Rotterdam criteria. In this study**,** Polycystic ovary was unilateral in 58 girls (48.73%) and bilateral in 61girls (51.27%). Among the 144 adolescents with PCOS, USS showed normal ovaries in 25 girls (17.36%). The association of polycystic ovaries with the other two criteria were tested. The different phenotypes identified in the 144 girls with PCOS include: Girls with menstrual irregularity and having polycystic ovaries on USS - 117 (81.25%), girls with clinical Hyperandrogenism and having polycystic ovaries on USS - 94 (65.27%) and girls having both menstrual irregularity and clinical hyperandrogenism without evidence of polycystic ovaries on USS - 115 (79.86%). All the three criteria were present in 91(63.19%) patients. The baseline characteristics of the study population are shown in table 1.

Further analysis was for association of PCO on USS with each of other variables. Out of the 141 girls with menstrual irregularities, USS detected PCO in 116 girls (82.97%). All three girls with regular cycles had normal ovaries (Figure 1). There was a significant association between presence of clinical hyperandrogenism and USS detected PCO in this study (p-0.044). Among the 144 adolescents, 118 were hyper androgenic clinically (81.94%) from whom 94 were positive for PCO on USS (79.66%). The study noted a significant association of hirsuitism with PCO ($p < 0.05$). Among the 144 adolescents with PCOS, 63 (43.75%) had FG score more than 8 and 44 (69.84%) among the 63 hirsuitism girls showed PCO on USS. Among the 119 adolescents positive for PCO on USS, only 44 were hirsuitism (36.97%). These values are much higher compared to reports in adult PCOS [11].

103 out of 119 (86.55%) PCO positive girls were overweight or obese and 82.4% of obese girls had PCO on USS. 88% of girls with normal ovaries reported high BMI. Statistical analysis showed p value more than 0.05 proving that association is not significant. Among the 144 adolescents with PCOS, 119 girls had ovaries with either increased volume or increased number of follicles or both, i.e., positive

for PCO on USS (82.63%). Overall, 96 girls had their ovaries >10ml in volume and 80 girls were reported to have follicle number >12 in their ovaries. Both findings were present in 50 adolescents and 25 girls had normal ovaries. Further, these 144 girls with PCOS were made into two groups - One group having PCO with increased ovarian volume only and the other group having PCO with increased follicle number only. PCO positive girls with enlarged ovaries (96 out of 144) constituted 66.7% and those with ovaries having follicle number >12, constituted 55.55% (80 out of 144).

Association of each PCOS phenotype was tested with enlarged ovaries and ovaries with >12 number of follicles, by separate statistical analysis. Significant association was noted between enlarged ovaries and MI (p value 0.013), as all 96 girls with enlarged ovaries in our study presented with irregular periods and the 3 girls without MI had normal volume ovaries. There was no significant association between enlarged ovaries and obesity or hyperandrogenism. Hirsuitism assessed by modified Ferriman Galway scoring showed significant association, with increased ovarian volume, as well as with follicle number more than 12.

Table 1: Baseline characteristics of the study population

	Mean
Age (years)	17.19
Body fat %	26.24
BMI (kg/m^2)	23.23
W/H ratio	0.87
Right OV (ml)	11
Left OV (ml)	9.36
FNPO (right)	2.95
FNPO (left)	2.71
FG score	6.57

BMI – Body Mass Index, W/H ratio – waist / hip ratio, OV - ovarian volume, FNPO - Follicle Number per ovary, FG - Ferriman Galway score for hirsuitism

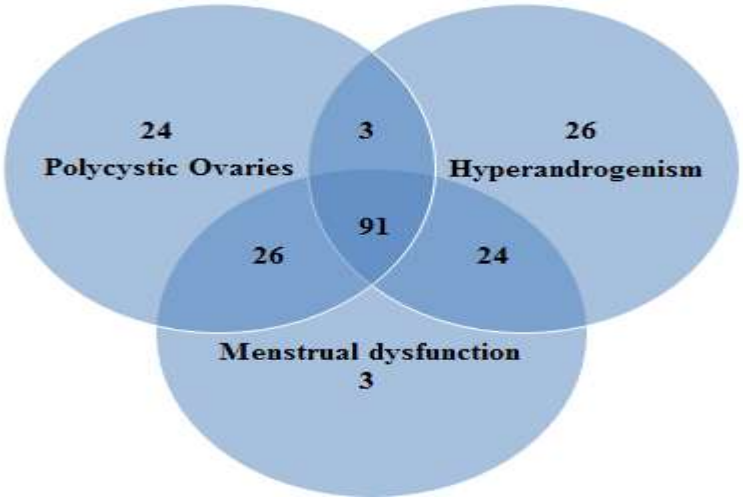

Fig 1: Distribution of polycystic ovaries, hyperandrogenism and menstrual dysfunction among the study population

DISCUSSION

The study included 144 adolescent girls with age range 15 to 19 years. The lowest age was set at 15 years, because irregular menstrual cycles in immediate post menarchal period are common problem and one inclusion criterion was menstrual

irregularity. It has been suggested that menstrual cycles lasting 40-45 days be considered normal until 2-3 years after menarche. However, 35 days for an upper limit of the menstrual interval may be more correct since prospective studies have shown that 98% of girls with cycles between 21 and 34 days have normal cycles during adult age whereas the same is true only for 66% of adolescent girls with cycles lasting 35-40 days.

Similar studies correlating the different phenotypic expressions of PCOS with obesity, hirsuitism, insulin resistance and various hormonal assays (Testosterone, DHEA-S, 17-OH progesterone, androstendione, FSH, LH, estradiol, Anti Mullerian hormone) in adolescence are available in literature. The present study included adolescents with clinical evidence of hyperandrogenism (presence of acne, acanthosis nigricans and severity scoring of hirsuitism); however, the biochemical analysis was not done in the present study. The other two inclusion criteria were chronic anovulation and presence of polycystic ovaries on USS. We followed the standard criteria for chronic anovulation and polycystic ovaries in selecting the study population. The girls who had any two out of the three criteria were included, (Rotterdam consensus) even though some authors propose that all criteria of the Rotterdam consensus are required for diagnosing PCOS during adolescence [8].

The role of ultrasound in diagnosing polycystic ovaries is well emphasized. The ultrasound scan is easily available, has no adverse effects on gonads, and can be repeated if needed. Using ovarian laparoscopy as the gold-standard, ultrasonography was calculated to have a sensitivity of 91% and a specificity of 100% in detecting polycystic ovarian morphology [1]. However it is subjective, depending on the operator and the machine. For diagnosing PCO, we used the ESHRE/ASRM consensus; an ovary with 12 or more follicles measuring 2–9 mm in diameter and/or an increased ovarian volume (>10 cm3). The newer criteria like follicle number >26 and >19 per ovary has been put forward by different authors recently [1, 21]. Owing to improvements in the resolution of ultrasound technology. More recent reports suggest anti-Mullerian hormone (AMH) to be more precise than ultrasound, with a threshold serum concentration of >35 pmol/l. However, this figure has not been universally accepted, and the use of AMH as a surrogate for follicle number is currently being debated [1, 22, 23].

In our study of 144 adolescents with PCOS, 97.91% presented with menstrual irregularity, 82.63% with PCO on USS and 81.94% with clinical hyperandrogenism. Slightly higher figures were noted in other studies: 90% in a Greek study [1]. Hickey *et al.;* in 2011 reported the prevalence of clinical, ultrasound and biochemical features of PCOS in a community-based adolescent population using current diagnostic criteria [7]. PCO was detected in 89.6 % girls diagnosed to have PCOS by Rotterdam criteria [17] comparable with the 82.63 % in the present study. Further analysis of PCO positive girls for increased ovarian volume and increased follicle number was not reported by them. They conclude that menstrual irregularity is common in adolescence and does not relate to clinical or biochemical HA and that diagnostic criteria for PCOS which include ovarian volume and morphology may be of limited use in adolescence.

A retrospective study of total number of 118, age-matched, young Turkish women with initial admission signs and symptoms of menstrual disorders like oligo/anovulation or hirsuitism, reported no significant difference found in terms of BMI or Ferrimann Galway score of >8 in patients with or without PCOS. Ovarian volume was higher in the PCOS group [22]. Irregular periods are a common symptom in adolescence. We included those girls between 15-19 years only and at least 2 years post menarchal, to exclude the possibility of irregular cycles in adolescent population. Literature review suggests menstrual irregularity not consistently associated with other features of PCOS. Polycystic ovaries were associated with persistence of oligomenorrhoea, and up to 90% of the oligomenorrhoeic population has polycystic ovaries at ultrasound [24]. In a study of 73 adolescents with menstrual irregularities, polycystic ovaries were detected in 41% and normal ovaries in 36% of the subjects while 23% had multifollicular ovaries. Their results tally with reports from Carmina *et al.;* where 40% incidence of polycystic ovaries is found in adolescents with menstrual irregularity [8]. Another study assessing ovarian morphology and size on ultrasound in adolescents with normal menses, estimates the prevalence of polycystic ovaries in the general population in the order of 20–33% [25]. All these reports suggest that there is considerable morphological ovarian variability in adolescents and insist on all 3 components of Rotterdam criteria for the diagnosis of PCOS in adolescents.

Literature review showed wide variation in the reported incidence of obesity in PCOS varying between 20-80% [26, 27]. The prevalence of hirsuitism and obesity following the criteria of FG score >8 and BMI category 3&4, respectively, was very less in the study by Hickey *et al.;* (8.3% and 43.7% compared to 43.75% and 86.55% in our study) [7]. The high association of increased BMI with PCOS in our study could be due to the modification in criteria used for classifying BMI in adolescents (Modified ELIZ chart for adolescents). According to this criteria, patients with BMI > 22 and > 25 were considered as overweight and obese respectively. For hirsuitism, the criteria used was same (FG score >8), still yielding significantly high value in our study. We used the most commonly employed scoring method of hirsuitism, (modified FG score) though subjective variability is reported as one of its drawbacks. To eliminate this error, all girls were examined by more than one gynaecologist, blinded to each other and results compared. Hirsuitism as presenting symptom of PCOS is uncommon in adolescents because it takes longer to develop in presence of androgen excess [7].

The association of polycystic ovarian morphology on ultrasound was tested with hirsuitism and found to be significant. Similar studies from literature show very high association of presence of PCO with clinical hyperandrogenism (92.31% compared to 79.66% in the present study) [10]. The association of PCO in hirsuitism can be attributed to the increased level of circulating androgens in them. The less common association of hirsuitism in those with PCO show that factors other than hyperandrogenism contributes to development of PCO in adolescents, in addition to delayed manifestation. There was no significant association between PCO and obesity in our study. Similar reports from a smaller study of 33 ethnically heterogenous American girls with PCOS diagnosed using NIH criteria, 22 of whom were obese, found no differences in ovarian morphology or volume between PCOS subjects and 13 obese controls support our findings [20]. The authors attribute this finding to the independent effect of LH and Insulin on ovarian volume. This could explain the comparable ovarian volumes seen in the non-obese and obese PCOS groups, because the former had higher LH and the latter greater fasting and stimulated insulin levels. Further analysis and statistical testing to look for association of ovaries with increased volume and ovaries with excess follicles with menstrual irregularity, hirsuitism and hyper androgenemia was undertaken. All girls with PCO on USS had menstrual irregularity, forming a significant association. Likewise both enlarged ovaries and ovaries with follicle excess have significant association with hirsuitism. Recently it has been shown by Principal Component Analysis that the FNPO is one variable of the androgen component of PCOS having even better sensitivity than serum androgen measurements [1]. Therefore, the presence of PCOM may be regarded as a sign of hyperandrogenism and the same might apply for elevated serum AMH concentrations [1].

CONCLUSION

Polycystic ovarian syndrome is difficult to diagnose in adolescent age group, even after decades of research. No definite criteria have been formulated so far. Since PCOS is considered as an endocrine disorder with far reaching consequences, early identification and treatment is mandatory in early years of life itself. Our study results are almost consistent with those reported in literature and points to the need for a more integrated approach for early diagnosis of this disorder. With development of various imaging modalities, visualisation and assessment of ovaries become more accurate which can help in redefining the diagnostic criteria further.

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