An Unusual Case of Fragile X Associated Primary Ovarian Insufficiency

Sir,

Premature ovarian insufficiency (POI) is defined as ovarian failure in women of age <40 years. Here is a report of an adolescent girl with few unusual features in a genetic POI.

A 20-year-old girl, presented with the complaints of attenuated breast development and scanty menstrual periods. At 18 years of age, after unsuccessful naturopathic treatment, she consulted a gynecologist for primary amenorrhea. Her FSH was 68 U/L and LH 46 U/L. Her karyotype was 46 XX in 30 metaphases and subsequently, she was started on combined oral contraceptive pills. She consulted us after 2 years as there was only mild improvement in symptoms.

Her maternal cousin had intellectual impairment by birth and expired at the age of 12 due to severe lung infection. Her brother was hyperactive since childhood. She weighed 52 kg and her height was 154 cm. She had normal mentation, elongated face with low set ears; breast - tanner 3, pubic hair - tanner 2, and labia majora was not fully developed. She had no features of autoimmunity or hepatosplenomegaly. She had no neurocognitive problems, behavioral or psychiatric disorders.

Karyotype was repeated with 50 metaphases, which again was normal. Triple repeat—primed polymerase chain reaction (TP-PCR) for detecting premutations in Fragile X Mental Retardation 1 (FMR-1) gene showed 134/151 CGG repeats [Figure 1a] and hence was diagnosed as Fragile X associated POI (FXPOI). She and her parents were counseled regarding limited fertility potential. She was started on daily estradiol valerate 1 mg in view of suboptimal breast development. Her parents and brother had normal repeats [Figure 1b].

Fragile X syndrome (FXS) is caused when there is expansion of CGG trinucleotides (>200) in untranslated region of FMR-1 and subsequent hypermethylation of CGG trinucleotides or CpG island.[1] Repeats between 55 and 200 are called premutations and results in FXPOI and fragile X associated tremor/ataxia syndrome (FXTAS).[2]

One-third of premutation carriers (PC) are thought to have FXPOI (includes varied phenotype like reduced AMH; increased FSH; oligomenorrhoea and early menopause). About 3% of girls with PC have oligomenorrhoea and <1% have cessation of menses during adolescence.[3] We were unable to find any reports of primary amenorrhea, though secondary amenorrhea with as few as 3 cycles been reported in adolescents.[4] The prevalence of PC was 2% in POI, 0.7% in early menopause, and 0.4% in controls.[5] The pathophysiology of FXPOI are (a) increased levels of expanded FMR1 mRNA causing gain-of-function toxicity; (b) repeat associated non-ATG translation causing intranuclear inclusions; (c) association with long non-coding RNA and antisense transcripts, and (d) increased transcriptional activity resulting in DNA damage.[2]

Expansion of premutation to full mutation usually occurs through woman and very rarely through men.[1] Here, both parents had normal repeats yet the girl had biallelic premutation. Whether such biallelic PC has a more profound effect on phenotype is not known. One important factor determining the instability of repeats, causing expansion, is AGG interruptions.

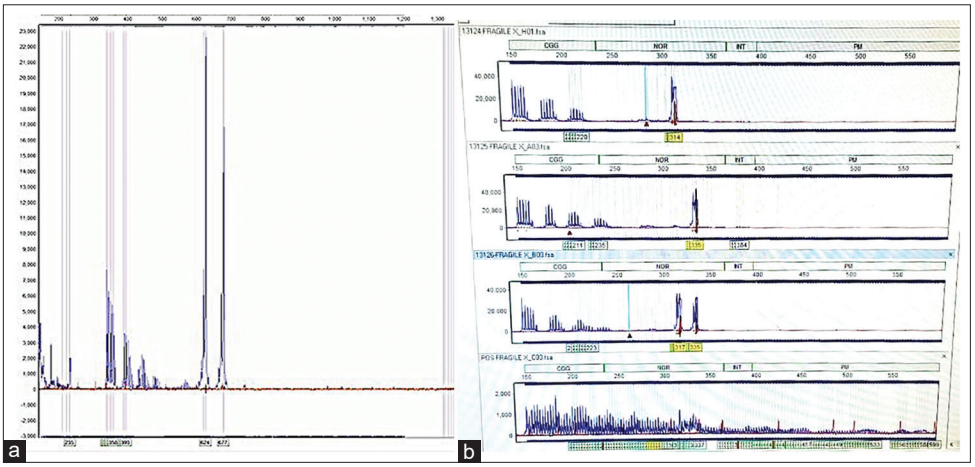

Figure 1: (a) Electropherogram of the proband showing detection of peak at 134/151 CGG repeats. (b) Normal electropherogram of the father (27 repeats), brother (35 repeats), and mother (29/35 repeats) of the proband

The unique features in this case were PC presentation as primary amenorrhea. Mid-range CGG repeats (80–99) is usually associated with FXPOI but in our case it was very much higher (134/151 repeats) than reported in literature.[3] Paternal expansion of repeats into PC was another distinguishing feature.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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