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Challenges in Diagnosing Permature Ovarian Failure

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Abstract

This is a case report of a single, 25 year old female of Asian origin, who was referred to the reproductive endocrinology clinic at St. Marys Hospital, Manchester with the initial diagnosis of Premature Ovarian Failure (POF) for manging her hormone replacement therapy. She had a complex medical history including a cerebellar pilocytic astrocytoma, excised at the age of 3, with supplementary radiotherapy. The diagnosis of POF was made at the age of 16 following history and investigation, primarily on the basis of amenorrhoea and low serum oestradiol levels. Hormonal profile was revisited and genital tract imaging was undertaken. The revised diagnosis of hypothalamic amenorrhoea had been overlooked which had major implications on future fertility. The principles of diagnostics and therapeutic measure are discussed.

Abbreviations

AMH: Antimullerain Hormone; FSH: Follicle Stimulating Hormone; LH: Luteinising Hormone; MDT: Multidisciplinary Team; POF: Premature Ovarian Failure

Patient History

Miss X was only 3 years old when she was diagnosed with a Cerebellar pilocytic astrocytoma. Initially, she underwent neurosurgery and further radiotherapy and chemotherapy.

Secondary to this she unfortunately developed severe headaches and migraines caused by hydrocephalus and required multiple revisions of a Ventriculo-peritoneal shunt. As a result of her extensive neurosurgical history and the location of the lesion Miss X also suffered from left 4th cranial nerve palsy, however, this did not cause her any physical symptoms and, she has regular follow up by the ophthalmology team.

She subsequently went on to develop epilepsy secondary to the hydrocephalus. In additionally she was diagnosed with Reynaud's phenomenon and having Thalassemia trait. Miss X subsequently went on to develop secondary amenorrhoea and was referred initially to a paediatric endocrinologist. There was no relevant family history to note.

Multidisciplinary clinical (MDT) management

Miss X was part of a large MDT (multidisciplinary team) including neurosurgeons, neurologists, paediatric oncologists, paediatric endocrinologists and reproductive endocrinology gynaecologist she was initially assessed by the endocrinologist at the age of 16 to investigate her short stature – her height (146 cm) plotted on the 2nd centile, and weight (43.3 kg) on the 9th centile for her age and sex. At which time she divulged that since her menarche in 2003 aged 13; she subsequently had 1-2 normal menstrual cycles (5-6/28) and had been experiencing amenorrhoea since then. Miss X denies any inter-menstrual bleeding, and was not currently sexually active. On examination Miss

X had normal secondary sexual characteristics for her age and pubertal development was appropriate.

She was thoroughly investigated under the care of the paediatric endocrinologist from this point onwards in view of her amenorrhoea and previous neuro-oncology history (Table 1).

On the basis of the above results, she was diagnosed with Premature Ovarian Failure (POF), at the age of 23 in view of hypo-oestrogenaemia. She was commenced on Loestrin (combined oral contraceptive pill) as a way of hormonal therapy. A conversation was documented with the paediatric oncologist regarding the necessity for; 'assisted reproduction with the possibility of using her mother/sisters as egg donors in the future for conception'.

Reproductive endocrinology investigations

A referral was made to the reproductive endocrinology team at the age of 24 with a view to

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Table 1: Initial hormone profile.

	May 2013	Sept 2013	March 20 14	Reference Ranges [1]
FSH	12 IU/ml	8 IU/ml	6 IU/ml	Follicular phase (FP) 2.4 – 12.6 IU/l Menopausal >30 IU/L
LH	40 IU/ml	6 IU/ml	9 IU/ml	FP 3.5–12.5 IU/l
Oestradiol		85 pg/ml	86 pg/ml	FP 45–854 pmol/l

Table 2: Revisited hormone profile.

	May 14	Feb 15	June 15	Normal ranges [1]
FSH	5.4 IU/ml	6.6 IU/ml	8.1 IU/ml	FP 2.4 – 12.6 IU/l Menopausal 1.0 >30 IU/l
LH	9.5 IU/ml	7 IU/ml	8.6 IU/ml	FP 3.5–12.5 IU/l
Oestradiaol		149 pg/ml	169 pg/ml	FP 45–854 pmol/l
Prolactin		218 mIU/L		102-496 mIU/l
Testosterone		1 nmol//L		<1.5 nmol/l
SHBG		37 nmol/L		18 – 114 nmol/l
Free androgen		2.7 nmol/L		7 – 10 nmol/l
TFT		TSH 2 pmol/L		TSH 0.2 – 5 mu/l
		T4 19.7 pmol/L		T4 9 – 24 pmol/l

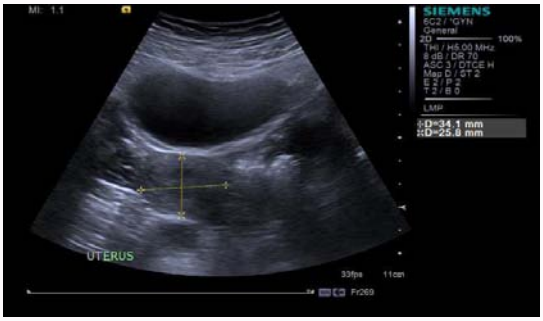

Figure 1: Pelvic USS March 2015 Uterine size 34.1 mm.

managing her hormonal replacement. Following a detailed history and examination, Miss X was further investigated; based on two principles. Firstly, to revisit the hormonal profile (Table 2) and secondly, to investigate genital tract development with pelvic ultrasound scan in view of the early onset of hypo oestrogenaemia.

Results

The results revealed; pituitary gonadotropins were within normal range. In addition, AMH (anti-Mullerain hormone) levels were also assessed and measured 41.95 pmol/l (7-70 pmol/l normal range), showing optimal ovarian reserve. Further discussion took place within the MDT, regarding the diagnosis of POF 'who were with the opinion that the results of all the above investigations supported the diagnosis of POF', primarily in view of the low oestradiol levels. The alternative diagnosis, of hypothalamic amenorrhoea, was initially rejected by the MDT in view of the normal (non-reduced) levels of pituitary gonadotrophins. The revised diagnosis was established as hypothalamic amenorrhoea. An ultrasound was performed confirming a small uterine size of 34.1 mm (Figure 1). There after dramatically changing the consequences and management plan for this young lady, who up until now was under the impression she would require In-Vitro Fertilization (IVF) and oocyte donation to conceive.

Management

The principle of our management was not only of providing oestrogen replacement but equally importantly of ensure genital tract maturity, in preparation for future assisted reproduction. Miss X was commenced on high dose oestrogen preparation to stimulate the growth and maturation of her uterus.

She had a course of 6 mg estradiol in the form of a long 90 days cycle, followed by two weeks of progestogen to induce withdrawal bleeding. Subsequent pelvic ultrasound scans were also performed to assess the genital tract, with regular follow up in the reproductive endocrine clinic.

On review of the repeat pelvic ultrasound scans; from March 2015 (Figure 1) to October 2015 (Figure 2) revealed an initial increase in uterine length from 34 mm to 56 mm and from October 2015 (Figure 2) to December 2015 (Figure 3) to a fully mature size of 76 mm, a size able to potentially carry a pregnancy (Figure 1-3). All ultrasound imaging revealed normal ovarian size.

Discussion

Young females presenting with amenorrhoea, whether primary or secondary, would be seriously concerned regarding their reproductive potential. Basic investigations usually include levels of serum oestradiol and the pituitary gonadotrophins; FSH and LH to investigate the pituitary ovarian axis, amongst other investigations to exclude alternative causes of amenorrhoea. The diagnostic criteria of POF, also know and premature ovarian insufficiency, were revised and recommended as; oligo/amenorrhea for at least 4 months, and an elevated FSH level >25 IU/l on two occasions >4 weeks apart

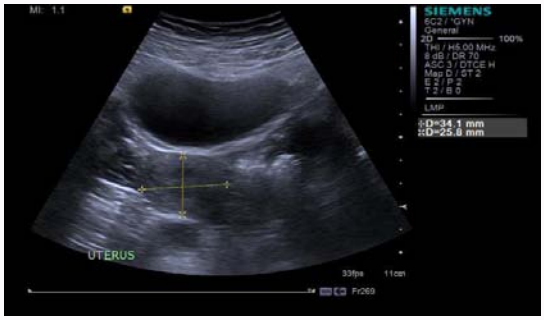

Figure 2: Pelvic USS October 2015 Uterine size 53 mm.

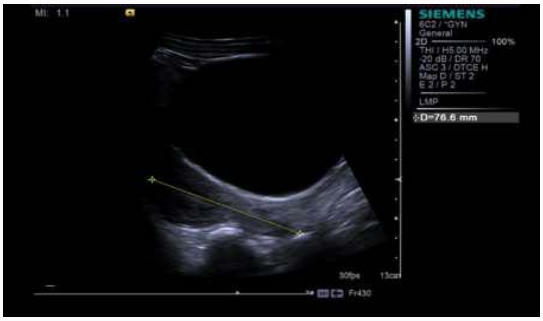

Figure 3: Pelvic USS December 2015 Uterine size 76 mm.

[1,2]. Clearly not evident in this case; hence the rejection of the initial diagnosis of POF.

POF occurs in 1% of the population and is commonly idiopathic [3]. The knowledge that as a young female you may not be able to conceive naturally can be devastating. On the other hand, hypothalamic amenorrhoea accounts for 34% of secondary amenorrhoea which is also associated with low serum oestradiol levels [4].

Consequently, it remains of great importance to appropriately interpret the result of FSH and LH to allow discriminating the two conditions which have important and different implications on future fertility. While the diagnosis of POF could be readily made by the elevated FSH and LH to menopausal levels, the levels of pituitary gonadotrophin in cases of hypothalamic amenorrhoea could well be misinterpreted. It has always been assumed that the levels should be low. However, Studies have shown that the absence of FSH elevation >10 IU/l, and the absence of LH elevation >6.5 IU/l is diagnostic of hypothalamic amenorrhoea [5]. In keeping with the non-elevated levels in this case.

It is well documented that in post cranial radiotherapy as a child, there can be deficient growth hormone levels. However it is less commonly documented regarding the possible thyroid and gonadal effects – as these are thought to come from high dose radiation. However it was shown that 70% of the females involved in a study in 1993 suffered from oligo menorrhoea, and 50% had hypo oestrogenaemia [6]. Proving more common than originally understood.

In young women presenting with hypo-oestrogenic status, the importance of ensuring full genital tract maturity is pertinent to achieving successful outcome of future assisted reproduction [7].

There have been studies to show the significant difference of uterine length between a control group and hypothalamic patients. In a study comparing BMI and various other outcomes, uterine length was 5.70 ± 0.79 cm in the hypothalamic group, compared to 7.31 ± 0.9 cm, a mature size in the control group [8]. This case reveals an extremely small uterine length at 3.4 cm on first measurement (Figure 1). To date, there has been no consensus regarding the appropriate hormonal regimen which is required to achieve full uterine growth.

In summary, the management of young females presenting with amenorrhoea and hypo-oestrogenaemia requires careful consideration with respect to the implications of the condition on future reproduction.

References

1. http://www.cmft.nhs.uk/media/1752922/combined%20user%20manual%20%20table%20of%20tests%20no%20sendaways.pdf. Last viewed 2/2/17.
2. European society of human reproductive and embryology Guideline Group on POI, Webber L, Davies M, Anderson R, Bartlett J, Braat D, et al. ESHRE Guideline: management of women with primary ovarian insufficiency. Hum Reprod. 2016; 31: 926-937.
3. Coulam CB, Adamson SC, Annegers JF. Incidence of premature ovarian failure. Obstet Gynecol. 1986; 67: 604-606.
4. Perkins R, Hall J, Martin K. Aetiology, previous menstrual function and patterns of neuroendocrine disturbance and a prognostic indicators in hypothalamic amenorrhoea. Human Reprod. 2001; 16: 2198-2205.
5. Jonard S, Pigny P, Jacquesson L, Demerle-Roux C, Robert Y, Dewailly D. The ovarian markers of the FSH insufficiency in functional hypothalamic amenorrhoea. Human reprod. 2005; 20: 101 -107.
6. Constantine L, Woolf P, Cann D, Mick G, Kenneth McCormick, Raubertas RF, et al. Hypo-thalamic pituitary dysfunction after radiation for brain tumours. N Engl J Med. 1993; 328: 87-94.
7. Meshki A, Seif M. Premature ovarian failure. Curr opin obstet gynaecol. 2006; 18: 418-426.
8. Bumbuliene Z, Klimasenko J, Sragyte D, Zakareviciene J, Drasutiene G. Uterine size and ovarian size in adolescents with functional hypothalamic amenorrhoea. Arch dis Child. 2015; 100: 948-951.