

A Primer on Pituitary Injury for the Reproductive Endocrinologist: Simmonds disease, Sheehan's syndrome, Traumatic injury, Dahan's syndrome, Pituitary Apoplexy and Lymphocytic Hypophysitis

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Introduction

The pituitary gland plays a critical role in reproduction. In response to the hypothalamus the anterior pituitary secretes prolactin, thyroid stimulating hormone (TSH), Adreno corticotropic hormone (ACTH), follicle stimulating hormone (FSH), luteinizing hormone (LH) and growth hormone. Dysregulation in these hormones often lead to reproductive failure. Therefore, understanding of the mechanisms of pituitary injury is critical for the reproductive endocrinologist. Several modes of pituitary injury have been noted. Their pathophysiology will be discussed so that a proper differential diagnosis can be developed and the resultant mechanism diagnosed.

Simmond's Disease

Simmond's disease is atrophy or destruction of the anterior lobe of the pituitary gland resulting in hypopituitarism often panhypopituitarism. Many mechanisms can cause it including any of the following.

Sheehan's Syndrome

Sheehan's syndrome was first described in 1937 [1]. Owing to the hormonal requirements of pregnancy and the post partum state the pituitary gland undergoes hypertrophy and is more susceptible to injury. The pituitary gland is supplied with blood from the circle of Willis, a vascular anastomosis caused by the confluence of the end-vessels of the right and left anterior middle and posterior cerebral arteries. This gland is also supplied internally by the superior and inferior hypophyseal arteries which are branches off the internal carotid. When a massive peri partum or post partum haemorrhage occurs, flow to these vessels is severely diminished and may lead to partial or complete infarction of the pituitary gland. Since the end vessels are supplying the circle of Willis this region is most at risk from the resultant hypotension. The damage of the gland may be further aggravated by a compensatory vasospasm or resultant thrombosis of these arteries [2,3]. However, thrombosis seems less likely due to the many vessels supplying the circle of Willis. Other causes of pituitary failure in pregnancy include severe head injury, subarachnoid haemorrhage, heart diseases, and massive

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stroke [3], all inducing severe hypotension. Non obstetrical causes of hypotension can also lead to a Sheehan's like presentation including, severe non-obstetric bleeding, liver disease and acute haemorrhagic fever [4-8]. In the developed world, the prevalence of Sheehan's syndrome has decreased significantly due to blood, volume expander and crystalloid transfusions. However, in developing countries where hospital care may be rarer and people have a tendency to deliver at home, Sheehan's seems to remain a persistent problem. In Kashmir, India, where most women deliver at home, a study found that 3.1% of all women had Sheehan's syndrome [9]. A Turkish study suggested that among 338 women studied with hypo pituitarism 28% had Sheehan's syndrome. This study found Sheehan's syndrome to be the second most common cause of pituitary dysfunction among women evaluated [10]. The diagnosis of Sheehan's syndrome is often missed with one study from the developed world finding that the average delay of diagnosis was slightly more than 9 years [11]. Sheehan's syndrome can have a variable presentation. Injury to the pituitary gland can result in pan hypopituitarism or may be partial, and very much depends on the quantity and location of the glandular injury. Occasionally the patient presents with diabetes insipidus within a few days of the haemorrhage, and the important diagnostic symptoms are polyuria and polydipsia.

In the case of pan hypopituitarism the immediate life threatening condition is hypocortisolism, with severe hypothyroidism being a delayed issue. In adults lack of growth hormone production fails to present with symptoms. Hypo prolactinemia will present with an inability to breast feed due to lack of lactation. Hypogonadotropic hypogonadism will present with prolonged amenorrhoea. Common symptoms include post-partum marked sensitivity to cold, mental apathy, physical weakness, somnolence, nausea, anorexia, and anaemia [12]. Sheehan's syndrome may present with rare signs and symptoms, such as hypoglycemia, hyponatremia, anaemia, pancytopenia, bradycardia, diabetes insipidus, headache, and loss of consciousness [12].

Traumatic Injury

Simmond's disease can be caused by pituitary injury due to severe haemorrhage in a non-pregnancy state, or by direct injury to the pituitary gland as part of a traumatic brain injury. Severe haemorrhage causing pituitary injury in non-pregnancy states is rarer than Sheehan's syndrome, which is most likely due to a smaller pituitary gland when women are not pregnant, so that it is not so susceptible to blood flow variations. This smaller gland has less hormonal requirements because of its non-pregnancy state and, as a result, it has increased tolerance to temporarily impaired blood flow. A recent study of people with severe traumas including head injury found that the prevalence of major anterior pituitary failure was 57% [13]. While in this series the occurrence of growth hormone deficiency was 40%, making it the most common hormone to be affected [13]. FSH and LH deficiency was 23%, TSH deficiency was 17% and ACTH deficiency occurred in 10% of subjects [13]. It has often been felt that pituitary injury post trauma may be overlooked because growth hormone seems to be the most common hormone affected and it will have little clinical implications in adults. Therefore, due to its lack of symptoms, diagnosis often is missed. Never the less, failure of menstrual cyclicity after a non-obstetrical trauma with blood loss should lead to an investigation for hypogonadotropism or other pituitary insufficiencies. Another mechanism of traumatic injury causing pituitary dysfunction is when that injury occurs to the brain. Such an injury affects the pituitary gland through direct trauma as well as by compromising the blood supply. It is only since the year 2000 that traumatic brain injury has been well recognized as a common cause of pituitary dysfunction, with few cases described before then. Between 15 and 50% of people with these injuries demonstrate affected pituitary glands [14]. Although, motor vehicle accidents are the most common cause of traumatic brain injuries [14] athletes are also at risk. Kick boxers have a 22.7% and 9.1%, incidence of GH and ACTH deficiencies, respectively [15]. Twenty-seven percent of kick boxers demonstrate at least one anterior pituitary hormone deficiency [15]. A recent study among ex professional American football players demonstrated that 19% had growth hormone deficiency while 9% had hypogonadism [16]. Irrelevant of the precipitating factor, people with traumatic brain injury should be followed for at least one year for the development of pituitary dysfunction to demonstrate [17].

Dahan's Syndrome

Dahan's syndrome is pituitary injury due to severe vasospasm, without significant haemorrhage [18]. The initial case presented in a woman with severe pre-eclampsia who was given bromocriptin to arrest lactation due to an intra-uterine foetal demise [18]. The women had minimal blood loss, and did not have a pituitary adenoma. However, severe vasospasm was noted to be occurring, in a normal size pituitary gland. Both pre-eclampsia and bromocriptin have been noted to induce vasospasm and whether the syndrome was due to one of these causes or a combination of both remains unknown. Although felt not to occur due to the protective effect of multiple arteries supplying blood to the pituitary gland, it makes intuitive sense that since the end arteries provide flow to this gland and severe hypotension can induce pituitary injury, it stands to reason that severe vasospasm may also injure the gland. In this case the patient presented with dysfunction in FSH, LH, prolactin, growth hormone and ACTH release. TSH release was normal [18]. The prevalence of this syndrome remains unknown since up until recently it was felt not to occur and may have been previously overlooked. It also remains unknown as to whether Dahan's syndrome occur in non-pre-partum states when the gland is less at risk to injury.

Pituitary Apoplexy

Pituitary apoplexy is infarction of a pituitary adenoma and intra-mass haemorrhage with result injury to hormone production by the gland. Recognized mechanisms of induction include overgrowth of the masses blood supply and spontaneous necrosis causing haemorrhage and infarction, or rupture of an intra-adenoma aneurism [19,20]. It has been postulated that pituitary macro adenomas have a high metabolic rate, poor blood flow and are susceptible to hypoglycemia which predisposed them to spontaneous infarction [20]. The intra-mass haemorrhage results in enlargement of the mass which compresses adjacent structures. Pituitary apoplexy typically presents as an acute episode of head ache, visual disturbance, cranial nerve palsies, and mental status changes. The resultant damage to the gland usually causes hormonal dysfunction. Although, likely under diagnosed since in many cases the pituitary adenoma is unknown the incidence of pituitary apoplexy is between 0.6 and 7% of pituitary masses [21-24]. The most common pituitary adenomas which resulted in apoplexy are non-functioning, growth hormone secreting, and prolactinomas, in that order [25]. Since pituitary injury has been noted in micro adenomas which lack the metabolic aggressiveness of macroadenomas the role of vasospasm in their development has yet to be determined. Hypopituitarism can be partial or complete at initial presentation. Endocrine dysfunction is very common at initial presentation, which is consistent with the fact that many of these patients had initially a macroadenoma which would affect hormone levels [26]. Posterior pituitary involvement is rare in pituitary apoplexy and therefore, diabetes insipidus is reported in only 3% of cases. Anterior pituitary hormone dysfunction however is present in about 80% of patients at initial presentation. ACTH deficiency occurs in about 70% of cases, and remains the most urgent life threatening event. TSH deficiency occurs in 50% of

subjects while 75% of patients lack FSH and LH, respectively [27-33]. Prolactin can be raised due to stalk compression or from an underlying prolactinoma [34]. It should be noted that low levels of prolactin at presentation are likely to predict residual hypopituitarism after definitive decompression [35].

Lymphocytic Hypophysitis

Lymphocytic infiltration is the most common cause of hypophysitis and the mechanism is often unknown, although it may be auto immune related [36,37]. It most commonly occurs in the post-partum period with one study noting that it occurred around pregnancy 63% of the time [37]. Although, a different study found conflicting results with most diagnoses coming independent of pregnancy [38]. Initially, it presents with enlargement of the pituitary gland particularly in the anterior region, followed by fibrosis and atrophy of the gland [37]. Spontaneous return of pituitary function may occur [36,37]. Hypogonadotropic hypogonadism is the most common presenting situation [38]. Deficiencies of other hormones can occur, as can diabetes insipidus [37,38,39]. Paradoxical hyperprolactinemia or growth hormone excess have also been noted [37,38,39].

Treatment

Management of these conditions in general involve replacement of the missing hormones. Growth hormone deficiency in adults is commonly ignored. Hypogonadism, requires replacement of estrogen and progesterone in a women, to prevent early

osteoporosis. Use of gonadotropins particularly follicle stimulating hormone and luteinizing hormone can be used to induce ovulation and pregnancy. After ovulation progesterone support should be provided to mimic the corpus luteum. Another option is low dose HCG 500 IU every three days to induce endogenous progesterone production. These traditionally would be continued until 10 week of pregnancy although stopping at four to six weeks gestational age may be an option. Replacement of thyroid hormone should be initiated. In the event of adrenal insufficiency both glucocorticoids and mineralocorticoids should be replaced. Low prolactin levels preventing lactation post-partum are managed with bottle feedings of formula or donor human milk. In the case of donor human milk, testing for blood borne disease should be undertaken, although it likely offers benefits above formula alone. Dosing of thyroid, glucocorticoid and mineralocorticoid replacement is complex and should be undertaken in conjuncture with a medical endocrinologist.

Conclusion

These clinical scenarios represent mechanism of pituitary injury which would interfere with reproduction particularly by preventing FSH and LH release. They are commonly overlooked, depending on hormones impacted can be life threatening and should be known to clinicians involved in reproduction. As more is known the relationship between these syndromes, pituitary apoplexy and there pathophysiology will become better understood.

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