Anterior Pituitary Hypofunction Following Aneurysmal Subarachnoid Hemorrhage: An Overlooked Clinical Syndrome

Yaqi Liu, Weijuan Cao
Xiangdong Hospital Affiliated to Hunan Normal University, Zhuzhou 412200, Hunan, China

Abstract: Subarachnoid hemorrhage (SAH) is a prevalent hemorrhagic cerebrovascular condition, often accompanied by complex and serious complications such as cerebral vasospasm, disseminated intravascular coagulation (DIC), cerebral edema, hydrocephalus, epilepsy, aneurysm rupture and re-hemorrhage, intractable hyponatremia, and acute glucocorticoid deficiency. These complications often lead to residual neurological deficits, severely affecting patients' quality of life. The most common cause of SAH is intracranial aneurysm rupture, specifically an aneurysmal subarachnoid hemorrhage (aSAH). As early as 1963[1], a neuropathological study demonstrated that 68% of patients who passed away soon after an intracranial aneurysm ruptured had extensive hypothalamic lesions. Several clinical studies that followed showed that a high percentage of patients with SAH who were examined between three months and a few years after the hemorrhage had partial anterior pituitary hypofunction (APH) , ranging from 37.5 to 55%[2]. This implies that the frequency of APH following aSAH has been underestimated. aSAH may result in permanent or transient pituitary insufficiency. Currently, there is a general lack of awareness of APH after aSAH. Its clinical manifestations are often insidious, making it difficult for clinicians to recognize, which frequently leads to missed or misdiagnosed cases. This review explores the pathophysiological mechanisms, epidemiology, diagnosis, and treatment of APH following aSAH, aiming to help clinicians better identify this condition, provide timely hormone replacement therapy, aid patient recovery, and improve quality of life.

***Keywords*:** aneurysmal subarachnoid hemorrhage; anterior pituitary hypofunction; pituitary hormone; hormone replacement

1. Introduction

About 5% to 10% of all stroke cases are subarachnoid hemorrhage (SAH), a type of stroke in which a blood vessel at the base of the brain or a superficial blood vessel of the brain ruptures, causing blood to leak into the subarachnoid space and causing a range of clinical symptoms. Intracranial aneurysm is the most common cause of SAH (85%)[3].

Anterior Pituitary Hypofunction (APH) is a clinical syndrome associated with injury to the pituitary gland, hypothalamus, or hypothalamus-pituitary pathway caused by multiple etiologic factors, resulting in decreased secretion of one or more pituitary hormones, which can involve adrenal glands, thyroid glands, and gonadal glands[4]. The prevalence of adult APH, also known as Simmound (Simon's) disease, has been reported in Europe to be 150-280 cases per 1 million[5].

2. Pathophysiologic mechanisms of APH after aSAH

A study published by M.R. Crompton as early as 1963[1] showed that hypothalamic lesions, including areas of ischemic necrosis, hemorrhage, and microhemorrhage, could be identified in 68% of patients. Aneurysms that rupture the anterior and posterior communicating arteries are more likely to be combined with hypothalamic lesions than aneurysms at other sites. For aneurysms near the midline, bilateral hypothalamic lesions are usually observed.

There is no clear-cut pathophysiologic mechanism for the APH that occurs after aSAH. Traumatic brain injury has been linked to a variety of mechanisms, such as mechanical injury to the pituitary region, hypothalamus, or pituitary stalk, vascular or hypoxic damage to the pituitary region and hypothalamus, changes in the inflammatory response and compressive effects brought on by hemorrhage, edema, or elevated intracranial pressure, as well as genetic susceptibility and autoimmune responses[6]. However, aSAH is known to be significantly less common. aSAH is followed by secondary APH, the mechanism of which has multiple anatomical and pathologic bases[7]. First, the Ring of Willis and the hypothalamic-pituitary complex show spatial proximity in the anatomy of the skull base, an anatomical feature that makes the pituitary tissue more susceptible to intracranial vascular lesions. Secondly, the pathophysiological changes triggered by SAH can impair pituitary function through multiple mechanisms: first, the aneurysm tumor directly exerts occupational compression on the pituitary stalk or pituitary gland, resulting in impaired blood flow in the portal venous system and hormone-secreting cell damage; second, the acute stage of the intracranial pressure rises dramatically causing vasospasm in hypothalamic-pituitary region, resulting in local microcirculatory disorders and ischemic necrosis; third, the acute stage of the intracranial vascular disease is caused by the craniotomy operation on the pituitary stalk mechanical pulling of the pituitary stalk by craniotomy operations, tissue

damage during hematoma removal, and negative feedback suppression of the hypothalamic-pituitary axis by drugs such as glucocorticoids; and fourth, local inflammatory reactions can be induced by hemolytic products after hemorrhage, which exacerbate the oxidative stress injury of pituitary cells and the dysfunction of the neuroendocrine network.

3. Epidemiology of APH after aSAH

Globally, the prevalence of APH following aSAH varies greatly, and some research has produced contradictory findings. The majority of research has divided aSAH into acute and chronic stages, with the first six months following the event being considered the acute phase and the six months following the event as the chronic phase. According to a systematic review and meta-analysis, the prevalence of APH following a SAH was 25.6% during the chronic phase and 49.3% during the acute phase[8]. Another meta-analysis reported a prevalence of 31% for Pituitary Dysfunction (PD) in the acute phase and 25% for PD in the chronic phase after aSAH. However, these two studies have been published for more than eight years, and in a recent systematic evaluation and meta-analysis reported that the overall prevalence of aSAH was 49.6% in the acute phase and 30.4% in the chronic phase, and that among hormone deficiencies, growth hormone dysfunction was the most common in the acute phase at 36.0%, while hypoadrenalism was most common in the chronic phase at 21.0%[9]. Growth Hormone Deficiency (GHD) is relatively common following aSAH, according to the majority of studies. Adrenocorticotropic Hormone (ACTH), gonadotropin, and thyroid stimulating hormone (TSH) are next in line. The incidence of APH was found to be largely constant across the three meta-analyses. Nearly half of patients with acute-phase aSAH and 25% of individuals with chronic-phase aSAH had APH.

4. Diagnosis and treatment of APH after aSAH

There is no clear statement on whether patients with APH after aSAH need to be evaluated for pituitary function and when to undergo pituitary function testing and hormone replacement because clinical predictors of neuroendocrine dysfunction after aSAH have not been identified and because of the lack of data on hormonal disturbances in the acute phase after aSAH. However, the diagnosis of adrenal insufficiency should not be missed during the acute phase of aSAH because it can be life-threatening. Patients need to be screened for signs, symptoms, and laboratory tests for hypocortisolism, including hyponatremia, hypotension, and hypoglycemia[10].

Due to the nonspecific nature of APH symptoms, there is a need to correlate the degree of abnormality with hormone testing. Detection of adrenal insufficiency in the setting of acute aSAH should be treated immediately as it may affect early prognosis. Treatment of secondary hypoadrenalism and hypothyroidism is essential. However, gonadal insufficiency is temporary during the acute phase of aSAH, and there is no conclusive proof that replacement hormones are required during this time. Sex hormone supplements should be used if hypogonadism continues during the chronic period. The patient's symptoms, age, and underlying condition should all be taken into consideration when treating GHD. Kreitschmann-Andermahr I et al. also suggested that patients with SAH have their endocrine function evaluated at three months and a year following the acute episode. Sequential glucocorticoid and thyroid hormone replacement therapy is necessary if central hypothyroidism and severe adrenocorticotropic hormone deficit are diagnosed.

5. Conclusion

In conclusion, the prevalence of APH after aSAH is higher than we have recognized. Despite the overlap between some of the clinical manifestations after aSAH and the symptoms of untreated APH patients, it can still suggest neuroendocrine dysfunction as a cause of injury in aSAH patients. Therefore, early recognition is crucial, and clinicians should raise awareness of APH after aSAH, actively assess pituitary function in post-SAH patients, and administer hormone replacement accordingly to promote recovery as well as improve patients' quality of life.

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