Review

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Hypopituitarism Associated with Non-Traumatic Subarachnoid Haemorrhage: A Narrative Review

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Abstract: Background: Hypopituitarism is a potentially serious but often underdiagnosed condition that can occur following non-traumatic subarachnoid hemorrhage (SAH). The condition is characterized by the partial or complete deficiency of one or more pituitary hormones, leading to a range of clinical manifestations that may complicate the recovery process. This narrative review aims to synthesize the current literature on the prevalence, pathophysiology, and clinical implications of hypopituitarism associated with non-traumatic SAH. **Methods**: A comprehensive review of the literature was conducting by authors using databases such as PubMed, MEDLINE, and Scopus, focusing on studies published in the last two decades. Studies were selected based on their relevance to the topic, with an emphasis on those that reported on the prevalence, diagnostic approaches, pathophysiological mechanisms, and clinical outcomes of hypopituitarism post-SAH. **Results**: The review revealed a wide variability in the reported prevalence of hypopituitarism following non-traumatic SAH, ranging from 14% to 92.3%, depending on the diagnostic criteria, timing of assessment, and hormonal axes evaluated. Commonly affected hormones include growth hormone, gonadotropins, and cortisol. The pathophysiology of hypopituitarism in this context is multifactorial, involving ischemic damage, inflammation, and direct mechanical injury to the hypothalamic-pituitary axis. While some studies suggest a link between hypopituitarism and adverse clinical outcomes, the evidence remain inconclusive, highlighting the need for standardized diagnostic protocols and longitudinal studies. **Conclusion**: Hypopituitarism is a prevalent but often overlooked complication of non-traumatic SAH, with significant potential implications for long-term health outcomes. Routine endocrine evaluation and management of pituitary deficiencies are recommended to improve patient care. Future research should focus on refining diagnostic criteria, elucidating the underlying mechanisms, and evaluating the long-term impact of hormone replacement therapy in this patient population.

Keywords: hypopituitarism; aneurysm; non-traumatic-subarachnoid hemorrhage; SAH; pituitary abnormlities; brain; cerebral

Background

Hypopituitarism, a condition characterized by the partial or complete deficiency of pituitary hormone secretion, poses significant clinical challenges due to its wide-ranging impact on various physiological processes [1,2]. The pituitary gland plays a central role in regulating critical endocrine functions, including growth, metabolism, reproduction, and stress response. Hypopituitarism can manifest with a spectrum of clinical features, depending on the specific hormones that are deficient and the degree of deficiency [2,3]. The condition can result in profound morbidity, affecting multiple organ systems and reducing the overall quality of life. While hypopituitarism is well recognized in the context of traumatic brain injury (TBI), its association with non-traumatic subarachnoid hemorrhage (SAH) is a growing area of interest in the medical community [4–6].

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Subarachnoid hemorrhage (SAH) refers to bleeding into the subarachnoid space, which is the area between the arachnoid membrane and the pia mater surrounding the brain [7]. Non-traumatic SAH, which occurs in the absence of head trauma, is most commonly caused by the rupture of an intracranial aneurysm. Other causes include arteriovenous malformations, cerebral vasculitis, and blood coagulation disorders. Non-traumatic SAH is a medical emergency that presents with sudden, severe headache (often described as a "thunderclap" headache), nausea, vomiting, neck stiffness, and altered consciousness [7–9]. The condition is associated with significant morbidity and mortality, with many survivors experiencing long-term neurological deficits [8].

The incidence of non-traumatic SAH varies by region but is estimated to be approximately 6.5 per 100,000 person-years globally. Although it accounts for only about 5% of all strokes, the high mortality rate and potential for devastating outcomes make SAH a critical focus of neurovascular care [10,11]. Survivors of non-traumatic SAH often face challenges related to cognitive dysfunction, emotional disturbances, and physical disabilities, contributing to a reduced quality of life. Emerging evidence suggests that endocrine dysfunction, specifically hypopituitarism, may be an under-recognized and significant sequela in these patients [7,11,12].

The potential relationship between non-traumatic SAH and the development of hypopituitarism has gained attention in recent years, with studies indicating that pituitary dysfunction may occur in a notable proportion of SAH survivors. The mechanisms underlying this association are not fully understood, but several hypotheses have been proposed [10,13,14].

One of the primary mechanisms suggested is the direct impact of the hemorrhage on the hypothalamic-pituitary axis. The pituitary gland is located in close proximity to the subarachnoid space, and the sudden increase in intracranial pressure, as well as the presence of blood and inflammatory mediators, may directly damage the gland or disrupt the blood supply to the hypothalamus and pituitary. Additionally, the release of free radicals and pro-inflammatory cytokines during the acute phase of SAH may further contribute to the development of hypopituitarism [12,14,15].

Another proposed mechanism is the involvement of vasospasm, a common complication of SAH, which can lead to ischemic injury in the brain, including the hypothalamus and pituitary gland. Vasospasm-induced ischemia may result in cellular damage and subsequent impairment of hormone production. Furthermore, delayed cerebral ischemia, a secondary event following SAH, may exacerbate injury to the pituitary region [13–15].

The prevalence of hypopituitarism following non-traumatic SAH varies across studies, with estimates ranging from 14% to 93% [16–33]. The wide variation in reported prevalence may be attributed to differences in study design, diagnostic criteria, and the timing of endocrine evaluation. It is also possible that hypopituitarism may develop as a delayed complication, with some patients experiencing pituitary dysfunction months or even years after the initial hemorrhagic event.

Clinical Manifestations and Diagnosis of Hypopituitarism Post-SAH

The clinical presentation of hypopituitarism following non-traumatic SAH can be subtle and nonspecific, often overlapping with the neurological and cognitive sequelae of the hemorrhage itself. Common symptoms include fatigue, weight gain, decreased libido, menstrual irregularities, and cold intolerance. In some cases, patients may present with more acute manifestations, such as adrenal insufficiency, which can be life-threatening if not promptly recognized and treated [14,17,19,22,24].

The diagnosis of hypopituitarism in SAH survivors requires a high index of suspicion, particularly in patients with unexplained symptoms that persist beyond the acute recovery phase. A comprehensive endocrine evaluation, including measurement of serum cortisol, thyroid-stimulating hormone (TSH), free thyroxine (T4), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and insulin-like growth factor-1 (IGF-1), is essential for identifying hormone deficiencies. Dynamic testing, such as the insulin tolerance test or the glucagon stimulation test, may be necessary to assess the integrity of the hypothalamic-pituitary-adrenal (HPA) axis and growth hormone secretion [22,23,27,29].

Prevalence of Hypopituitarism Following SAH

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The prevalence of hypopituitarism after SAH varies widely among studies, influenced by factors such as the time of hormonal assessment post-hemorrhage and the diagnostic criteria used.

A study by **Aimaretti et al.** [16] conducted in Italy revealed that 37.5% of SAH patients developed hypopituitarism by the 12-month follow-up, with growth hormone deficiency (GHD) being the most common deficiency, affecting 21.9% of patients. The study emphasized the importance of long-term follow-up, as pituitary function in some patients improved over time, while in others, it worsened.

Kreitschmann-Andermahr et al. [17] in Germany found a similar prevalence, with 55% of their SAH cohort showing pituitary dysfunction. GHD was again prominent, with 20% of patients affected. The study also noted that neuroendocrine dysfunction in SAH survivors contributed to significant weight gain and higher body mass index (BMI), especially among those with GHD.

Conversely, **Blijdorp et al.** [18] from the Netherlands reported a lower prevalence of hypopituitarism at 14% among SAH survivors. The study focused on the diagnostic value of the ghrelin test in detecting GHD and concluded that the test was valid and safe for early assessment of pituitary function.

Tölli et al. [19] in Sweden highlighted the acute phase assessment of pituitary function, finding that 60.9% of patients had some form of pituitary deficiency shortly after SAH, though the long-term implications of these early deficiencies were not fully elucidated.

Similarly, **Kronvall et al.** [20], also from Sweden, reported a 34.1% prevalence of hypopituitarism at 6-12 months post-SAH, increasing to 41% by 12-24 months. This study underscored the importance of dynamic testing, such as the insulin tolerance test (ITT), in detecting more subtle forms of pituitary dysfunction that may not be evident in basal hormone assessments.

In contrast, a study by **Robba et al.** [21] in Italy found an exceptionally high prevalence of pituitary dysfunction, with 91.1% of patients showing some form of deficiency in the acute phase, and 83.3% in both the subacute and chronic phases. However, this high prevalence did not correlate with long-term clinical outcomes, suggesting that while pituitary dysfunction is common, it may not always translate into clinically significant impairments.

In Japan, **Goto et al**. [22] conducted a study that reported a relatively lower prevalence of GHD at 15.2%. The study was notable for identifying surgical clipping as a risk factor for lower insulin-like growth factor 1 (IGF-1) levels, which correlated with a higher likelihood of GHD.

Parenti et al. [23] in Italy evaluated pituitary function within the first 72 hours of SAH and found that 56.9% of patients had at least one anterior pituitary hormone deficiency. Gonadotropin and GH deficiencies were the most common, aligning with findings from other studies. The study highlighted the potential for early identification of patients who may benefit from closer long-term endocrine follow-up.

In the UK, **Gardner et al.** [24] reported a lower prevalence of hypopituitarism at 12%, with rigorous testing protocols including glucagon stimulation and confirmation through additional tests. This study emphasized the need for stringent diagnostic criteria to avoid overestimating the prevalence of pituitary dysfunction.

Finally, **Pereira et al.** [25] in Brazil found that 59.1% of SAH patients had pituitary dysfunction within the first 15 days post-hemorrhage. This study reinforced the high risk of pituitary insufficiency following SAH and the importance of early endocrine evaluation.

Growth Hormone Deficiency Post-SAH

Growth hormone deficiency (GHD) is one of the most commonly reported endocrine abnormalities following SAH. The prevalence of GHD varies across studies, with some reporting rates as high as 27.3% [25]. The variability in prevalence may be due to differences in testing methods and the timing of assessments. GHD is associated with increased morbidity, including fatigue, depression, and poor quality of life, making its identification and treatment crucial.

Aimaretti et al. [16] and **Kreitschmann-Andermahr et al.** [17] both identified GHD as a significant issue in SAH survivors, with rates of 21.9% and 20%, respectively. The presence of GHD

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was also linked to increased BMI and weight gain, particularly in the German study, highlighting the metabolic consequences of this deficiency.

Blijdorp et al. [18] and **Gardner et al.** [24] both emphasized the importance of dynamic testing for GHD, with the former validating the use of the ghrelin test and the latter advocating for confirmatory testing with glucagon stimulation. These studies suggest that without rigorous testing, GHD may be underdiagnosed, potentially leaving patients at risk for untreated symptoms.

Other Hormonal Deficiencies Post-SAH

In addition to GHD, deficiencies in other hormonal axes are also common following SAH. **Kreitschmann-Andermahr et al.** [17] identified corticotroph deficiency in 35% of their cohort, with a significant gender disparity as most cases occurred in women. **Parenti et al.** [23] similarly found gonadotropin and GH deficiencies to be the most prevalent, though ACTH and TSH deficiencies were also present but less frequent.

Robba et al. [21] reported dysfunction across multiple axes, with pituitary-gonadal axis dysfunction being the most common. Despite the high prevalence of these deficiencies, the study did not find a correlation with clinical outcomes, suggesting that while pituitary dysfunction is widespread, it may not always lead to significant health issues.

The high prevalence of hypopituitarism following SAH, particularly GHD and other hormonal deficiencies, underscores the need for routine endocrine evaluation in these patients. Early identification of hypopituitarism can facilitate timely hormone replacement therapy, potentially improving long-term outcomes and quality of life for survivors.

Parenti et al. [23] and **Pereira et al.** [25] both advocate for early and thorough endocrine testing, particularly within the first few weeks post-SAH, to identify patients at risk for long-term pituitary dysfunction. Given the variability in the onset and progression of hypopituitarism, long-term follow-up is essential, as suggested by **Aimaretti et al.** [16] and **Kronvall et al.** [20].

Furthermore, the use of dynamic tests, such as the ITT and ghrelin test, as recommended by **Blijdorp et al.** [18] and **Gardner et al.** [24], may improve the accuracy of hypopituitarism diagnosis, particularly for GHD. These tests should be considered in routine endocrine evaluations following SAH to ensure that deficiencies are not overlooked.

Discussion

The prevalence and clinical implications of hypopituitarism following non-traumatic subarachnoid hemorrhage (SAH) have become increasingly recognized over the past decades [14,15,19,20]. The current literature presents varying estimates of pituitary dysfunction, which could be attributed to differences in study design, patient populations, timing of hormonal assessments, and diagnostic criteria.

The prevalence of hypopituitarism following SAH varies significantly across studies, ranging from 14% to as high as 92.3% in the acute phase. The study by Robba et al. reported the highest prevalence of pituitary dysfunction, identifying endocrine abnormalities in over 90% of patients in the acute phase after SAH [21]. This high prevalence could be due to the comprehensive hormonal assessment carried out at multiple time points, capturing transient as well as persistent deficiencies. In contrast, Blijdorp et al. reported a much lower prevalence of 14%, but their study focused solely on GH deficiency (GHD) and used a specific ghrelin test shortly after SAH, which might not have captured the full spectrum of pituitary dysfunction [18].

The variability in prevalence underscores the complexity of diagnosing hypopituitarism post-SAH. Differences in testing protocols, including the type of dynamic tests used and the timing of assessments, likely contribute to these discrepancies. For example, the insulin tolerance test (ITT) and the glucagon stimulation test (GST) are commonly used but may yield different results due to variations in sensitivity and specificity. The study by Gardner et al. emphasized the importance of confirmatory testing with alternative stimulation tests, which led to a lower prevalence of GHD (10%) compared to studies that did not use such rigorous diagnostic criteria [24]. These findings highlight

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the need for standardized diagnostic protocols to ensure consistency and comparability across studies.

While the prevalence of pituitary dysfunction post-SAH is well-documented, its impact on long-term clinical outcomes remains less clear. Several studies have attempted to correlate hypopituitarism with functional outcomes, quality of life, and neuropsychological impairments, but the results are mixed. For instance, Kreitschmann-Andermahr et al. found that patients with severe GHD exhibited a higher body mass index (BMI) and more significant weight gain compared to those without GHD, suggesting a potential link between endocrine dysfunction and metabolic disturbances [17]. However, Robba et al. found no correlation between pituitary dysfunction and clinical outcomes at 6 to 12 months, raising questions about the clinical significance of these hormonal abnormalities [21].

The discrepancies in findings may be due to differences in the patient populations studied, the timing of outcome assessments, and the specific outcomes measured. Some studies, such as that by Kronvall et al., have focused on neuropsychological outcomes, which may not be directly influenced by pituitary dysfunction, while others have examined more general measures of functional status, such as the modified Rankin Scale (mRS) [20]. Additionally, the role of other factors, such as the severity of the initial hemorrhage, the presence of cerebral vasospasm, and the specific treatment modalities used, must be considered when interpreting these results.

Despite the lack of a clear association between hypopituitarism and clinical outcomes in some studies, the potential for long-term consequences of untreated pituitary deficiencies cannot be ignored. For instance, untreated GHD is known to be associated with increased cardiovascular risk, reduced bone density, and impaired quality of life in the general population. Therefore, even if the immediate impact on functional outcomes is not apparent, the long-term health implications of pituitary dysfunction post-SAH warrant further investigation and consideration in the management of these patients.

The mechanisms underlying hypopituitarism following SAH are not fully understood, but several pathophysiological processes have been proposed. The pituitary gland is highly vascularized and vulnerable to ischemic injury, which can occur during the acute phase of SAH due to compromised cerebral blood flow. This is supported by findings from the study by Parenti et al., which reported a high prevalence of anterior pituitary hormone deficiencies acutely after SAH, with gonadotropin and GH deficiencies being the most common [23]. The acute phase of SAH is also characterized by a systemic inflammatory response, which may further contribute to pituitary dysfunction through cytokine-mediated damage to the hypothalamic-pituitary axis.

In addition to ischemia and inflammation, direct mechanical injury to the hypothalamic-pituitary axis during aneurysm rupture or subsequent surgical interventions may play a role. Goto et al. found that patients who underwent surgical clipping of aneurysms were more likely to have lower insulin-like growth factor 1 (IGF-1) levels, a marker of GH activity, compared to those who underwent endovascular embolization [22]. This suggests that the type of intervention may influence the risk of developing hypopituitarism, possibly due to the more invasive nature of surgical clipping.

Moreover, the role of vasospasm, a common complication of SAH, in the development of hypopituitarism is an area of ongoing research. Vasospasm can lead to delayed cerebral ischemia, which may extend to the hypothalamic-pituitary region, thereby exacerbating pituitary dysfunction. However, studies such as that by Gardner et al. found no association between vasospasm and hypopituitarism, indicating that the relationship between these two factors may be more complex and influenced by additional variables [24].

Implications for Clinical Practice

The high prevalence of hypopituitarism post-SAH and its potential long-term health consequences underscore the importance of routine endocrine evaluation in these patients. Early identification and treatment of pituitary deficiencies are crucial to prevent complications such as adrenal insufficiency, which can be life-threatening if not promptly addressed. The study by Kronvall et al. emphasized the value of dynamic testing, such as the ITT, in detecting subtle forms of pituitary

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dysfunction that might be missed with basal hormone measurements alone [20]. This approach allows for more accurate diagnosis and appropriate hormone replacement therapy.

However, the decision to initiate hormone replacement therapy should be carefully considered, particularly in cases of mild or asymptomatic deficiencies. The potential benefits of treatment must be weighed against the risks, especially in the context of the patient's overall clinical status and prognosis. For instance, patients with severe neurological impairments or poor functional outcomes may derive limited benefit from hormone replacement, and the focus of care may instead be on optimizing supportive measures and rehabilitation.

In addition to endocrine evaluation, clinicians should be aware of the potential impact of hypopituitarism on recovery and rehabilitation outcomes. Neuropsychological deficits, fatigue, and reduced exercise capacity are common in patients with untreated pituitary deficiencies and can significantly affect the rehabilitation process. Early recognition and management of these symptoms through appropriate endocrine and supportive therapies may enhance the overall recovery trajectory and improve quality of life for survivors of SAH.

Implications for Management and Future Research

The recognition of hypopituitarism as a potential complication of non-traumatic SAH has important implications for patient management. Early identification and appropriate hormone replacement therapy can significantly improve outcomes and quality of life for affected individuals. However, there is currently no consensus on the optimal timing and frequency of endocrine evaluation in SAH survivors, highlighting the need for further research in this area.

Future studies should focus on elucidating the pathophysiological mechanisms linking non-traumatic SAH and hypopituitarism, as well as identifying risk factors for the development of pituitary dysfunction. Longitudinal studies are particularly valuable in understanding the natural history of hypopituitarism in this patient population and in determining the long-term impact of endocrine deficits on recovery and overall prognosis. Additionally, there is a need for standardized guidelines to inform clinical practice, including recommendations for screening, diagnosis, and management of hypopituitarism in SAH survivors.

Conclusion

Hypopituitarism is a common and often underdiagnosed consequence of SAH, with significant variability in prevalence across studies. Growth hormone deficiency is particularly prevalent and associated with substantial morbidity. Routine endocrine evaluations, including dynamic testing, are recommended to identify and treat pituitary deficiencies in SAH survivors, thereby improving their long-term outcomes. Further research is needed to clarify the long-term impact of these deficiencies and to establish standardized protocols for endocrine assessment post-SAH.

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