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Systematic review

Infectious Causes of Hypopituitarism in Children: A Systematic Review

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Abstract

Objective: Infection causing pediatric hypopituitarism is rare but potentially life-threatening and scarce evidence is available for clinicians. Here, we give a quantitative overview of the infectious causes of hypopituitarism in children, and systematically discuss symptoms and clinical signs as well as the extent of endocrinological recovery.

Methods: We conducted a systematic literature search in Embase, Medline (PubMed) and Web of Science Core Collection to identify all published pediatric cases of hypopituitarism caused by infection. We selected articles with use of predefined exclusion- and inclusion criteria. **Results:** We identified 43 cases of children with hypopituitarism due to infection. Tuberculosis (TBC) of the central nervous system and pituitary abscess were the most frequent etiologies (17 and 12 cases respectively), followed by meningitis and meningoencephalitis with various microorganisms involved (8 cases). Clinical manifestations were variable and depended on the affected hormonal axes and the causative infectious disease. The pituitary-adrenal and -thyroid axes were often disturbed hormonal axes during infection associated with hemodynamic instability. Follow-up was insufficiently reported but revealed persistent requirement of hormonal replacement therapy in 12 cases and complete pituitary recovery in only 4 cases. Death was reported in a total of 7 patients. **Conclusion:** TBC and pituitary abscess have been most frequently associated with pediatric hypopituitarism. However, the occurrence of pituitary insufficiency in septic children needs to be further quantified. Mortality and long-term morbidity are considerable and make awareness among physicians crucial. To better understand the incidence and outcome of hypopituitarism in the infections we discuss, prospective studies are required.

Keywords: Hypopituitarism; Child; Infection; Pituitary Abscess; Tuberculosis.

Introduction

Hypopituitarism is defined as a "diminution or cessation of secretion of one or more hormones from the anterior pituitary gland" [1]. Hypopituitarism can be congenital or acquired [2]. Causes of acquired hypopituitarism are diverse and include tumors, autoimmune disease, infiltrative disease, chemotherapy, radiation exposure, trauma, and infection [2]. In childhood, isolated and idiopathic growth hormone deficiency is the commonest form of pituitary hormone deficiency [2,3].

Early diagnosis of hypopituitarism in children is crucial. The pituitary gland produces hormones involved in growth, metabolism, reproduction, and homeostasis [2]. Symptomatology of hypopituitarism depends on which hormones are insufficiently secreted and the severity of deficiency [2]. Hypopituitarism may lead to urgent conditions such as hypoglycemia or adrenal crisis. Disorders in cognitive development, growth failure, excessive weight gain and delayed puberty are examples of long-term morbidity. Laboratory results should be carefully interpretated as end-organ hormone deficiencies may hide central depletion [2]. Magnetic resonance imaging is indicated when hypopituitarism is suspected [2].

Infectious causes of hypopituitarism in children are uncommon and have principally been reported in literature as case series and case reports. Infectious meningitis, encephalitis, and hypophysitis can lead to pituitary hormone deficiency [3]. Mycobacterium tuberculosis is a known causative microorganism [3]. Pituitary abscess is rare but potentially life-threatening [4]. Cases of hypopituitarism due to fungal infections of the sellar region are sporadic [4]. The occurrence of infectious diseases as a cause of pediatric hypopituitarism has not been systematically reviewed yet.

The aim of this systematic review is to give a quantitative overview of the infectious causes of hypopituitarism in children. We will also systematically discuss clinical signs and symptoms as well as the extent of endocrinological recovery after infection treatment. Informing clinicians about infection as a cause of hypopituitarism is important for adequate diagnosis. Putting into perspective the infectious causes of hypopituitarism may outline which infections should be included in the differential diagnosis when hypopituitarism is diagnosed in a child.

Materials and Methods

We searched for literature in Embase, Medline (PubMed) and Web of Science Core Collection whereby we used both MeSH terms and free text. The aim of the search was to identify all reported pediatric cases of hypopituitarism caused by infection. The complete search strategy can be found in Supplementary Table 1. Through database searching we found 6241 articles which after deduplication resulted in 3644 articles that were subsequently screened by title and abstract (Figure 1). Another 3 articles were identified through snowballing. A PRISMA flow diagram is shown in Figure 1.

We applied the following exclusion criteria: congenital hypopituitarism or infection, iatrogenic causes of infection or hypopituitarism developed post-operatively, conference abstracts and proceedings, reviews without additional case report or case series, articles of which the full text was either not available or only available in languages different from English or French, articles without sufficient methodology or case description, and irrelevant studies. To be included in this systematic review, the studies had to discuss hypopituitarism due to infection in patients aged 0 to less than 18 years old. In these studies, pediatric cases had to be reported in absolute numbers and separately from adult cases to make data extraction possible. Similarly, infectious causes had to be reported separately from other causes of hypopituitarism. Articles of which the full text was not available were excluded if title and abstract did not meet the inclusion criteria. However, where title and abstract met the inclusion criteria, full texts were requested from KU Leuven Library and assessed if available. Based on the aforementioned criteria, 3414 records were excluded. The full texts of the 230 remaining studies were then assessed for eligibility. Another 190 studies were excluded, leaving 43 primary studies for inclusion in this systematic review.

We critically evaluated each study on internal validity with specific attention given to the used hormonal tests and interpretation of their results. Case series of which we did not only extract clinical case information but also used the author's data-analysis were evaluated by using the quality assessment tools developed by NHLBI [5]. We collected following data: patient characteristics, specific pituitary deficiencies and symptoms and clinical signs at the time of hormonal evaluation, underlying infectious diseases, hormonal replacement therapies (HRT) and extent of recovery of pituitary function during follow-up. These data were listed in result-tables and discussed.

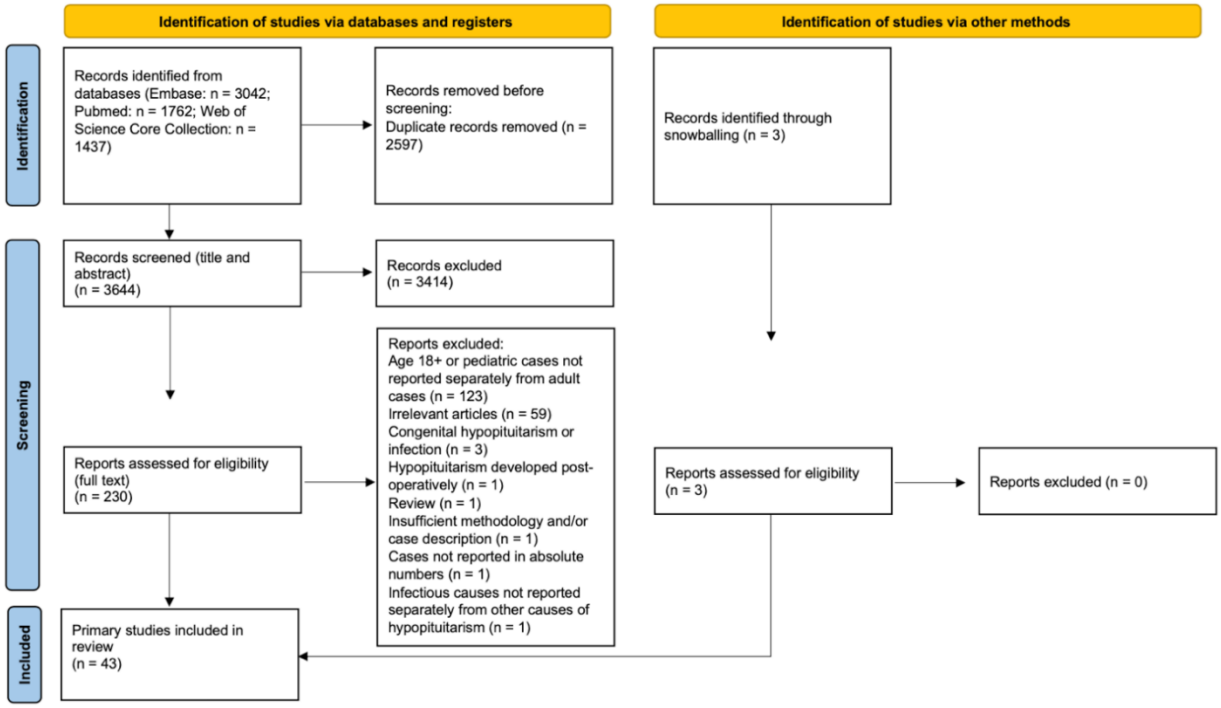

Figure 1: PRISMA flow diagram of the literature search. Figure adapted from Page et al. [6].

Results

In this systematic review, we present 43 cases of children with various infectious diseases that caused hypopituitarism. A summarizing overview is given in Table 1.

Tuberculosis of the central nervous system

We identified tuberculosis (TBC) of the central nervous system as the most common cause of acquired hypopituitarism due to infection. We included a total of 17 cases of TBC followed by hypopituitarism during childhood [7-22]. These cases are summarized in Table 1 and Supplementary Table 2, with description of specific pituitary deficiencies and symptoms and clinical signs at the time of hormonal evaluation. We also describe HRT and extent of recovery of pituitary function during follow-up.

TBC of the central nervous system principally occurred in the form of isolated tuberculous meningitis (TBM) (8 cases) [7-14]. Tubercular lesions additionally consisted of sellar and/or suprasellar tuberculomas (7 cases) [15-20]. We also report a case of tubercular abscess, located in the suprasellar region [21]. One diagnosis of TBC had not formally been established [22]. In this case, antitubercular treatment of 12 months was initiated in a context of a positive intradermal tuberculin test, abnormal MRI-imaging of the hypophysis, no evidence of other systemic granulomatous disease, and negative tumor markers in blood and cerebrospinal fluid. A pituitary biopsy was not judged necessary because of the benign course of the disease under antitubercular treatment.

Assessment of pituitary activity with hormonal tests led to the identification of various hormone depletions (Table 1 and Supplementary Table 2). Anterior pituitary dysfunction was associated with diabetes insipidus in most patients (10 cases) [8-10,12,13,15,16,19,21,22]. One child suffered from panhypopituitarism [21]. In 2 studies, authors suspected hypopituitarism to be secondary to hypothalamic dysfunction [12,14]. In 3 other studies, hypothalamic dysfunction was suspected to be the cause of the child's weight excess [7,16,20]. Arguments that supported the hypothesis of hypothalamic insufficiency were the suprasellar location of tubercular active lesions or sequelae and/or the results of hormonal tests using pituitary releasing hormones. For instance, in one case report, a significant increase in levels of adrenocorticotropic hormone (ACTH) in response to exogenous corticotropin releasing hormone suggested a deficiency of the latter hormone [14].

In cases of isolated TBM, without coexistent tuberculoma or abscess of the hypophysis, diagnosis of hypopituitarism was made months to several years after treatment of TBC. However, in all children who had a sellar and/or suprasellar tuberculoma, hormonal deficits were present at the time of diagnosis of tuberculoma. Four children with tuberculoma presented with non-endocrinological features such as headache, vomiting, and visual disturbances (decreased visual acuity and/or bitemporal hemianopsia) [16,18,19]. One of these children had fever [19]. It is important to notice that two patients had acute manifestations of central hypoadrenalism: a 3-year-old boy who developed hypoglycemia and a 15-year-old boy who suffered from shock secondary to mild diarrhea [11,12]. They both had a history of TBM.

In many articles, authors did not report if HRT was initiated, which hindered data analysis [8,9,11,14,17,18]. Moreover, 7 studies did not report any patient follow-up [9-11,13,14,17,19]. In other instances, follow-up often revealed persistent requirement of HRT (4 cases) [7,12,15,22]. In one boy, persistent requirement of HRT at 3 years of follow-up was associated with the discovery of 2 suprasellar tuberculomas [15]. Three children died and for one of them this was due to severe hypopituitarism with hypothermia and bradycardia, which are consequences of profound hypothyroidism [16]. In another child, death was suspected to be secondary to cessation of corticosteroids [21]. The third cause of death was not specified [8]. Finally, in no more than two studies, complete recovery of pituitary function was obtained [18,20].

Pituitary abscess

We identified 12 cases of pituitary abscess associated with hypopituitarism in childhood [23-33]. These cases are summarized in Table 1 and Supplementary Table 3.

At initial hormonal evaluation, anterior pituitary axes were variably deficient (Table 1 and Supplementary Table 3). Concomitant diabetes insipidus was diagnosed in 9 patients [23-27,29,30,33]. Four patients presented with panhypopituitarism [24,26,30]. A total of 3 abscesses developed in a pre-existing pituitary lesion [24,31,32]. These pituitary disorders were Rathke's cleft cysts in two children and adenoma in one child.

Most studies did not identify any risk factors for development of a pituitary abscess. Sinusitis was found to be a possible source of infection in 2 cases [25,33]. A 15-year-old girl was hospitalized for pneumonia one year prior to diagnosis of pituitary abscess [29]. Her pneumonia may have led to infection of the pituitary gland via hematogenous dissemination.

Bacteriological investigation was positive in 4 cases [25,29,31,32]. Following microorganisms were detected: Staphylococcus aureus (2 cases), Staphylococcus epidermidis (1 case), Streptococcus viridans (1 case), Streptococcus spp. (not further specified) (1 case), and Corynebacterium argentoratense (1 case). In 5 instances, cultures remained negative [24,27,28,30,33]. Only 2 of these patients received antibiotic therapy before samples were taken for culture [28,30]. For one of these 5 patients, the authors did not mention any antibiotic therapy at all besides surgery [24]. Individual bacteriological data were not available in 2 articles [23,26].

Duration of symptoms prior to presentation was variable. Symptoms were most often present for several weeks or months, with a maximum duration of 2 years [23,25-30,32]. Pituitary dysfunction was symptomatic in the majority of children (10 cases) [23-27,29,30,32,33]. Headache was the commonest symptom not related to endocrine disturbances and was present in 9 children [23,25,26-29,31-33]. Remarkable is that only one patient had fever [33]. Biological markers of inflammation, such as leukocytosis with an elevated count of neutrophils, elevated C-reactive protein and/or erythrocyte sedimentation rate were positive in 4 cases [23,27-29].

Three children had acute symptoms, such as altered consciousness, emesis, neck pain, and visual disturbances [28,29,33], suggestive for additional meningitis, encephalitis, and/or intracranial hypertension. An 11-year-old boy had bitemporal hemianopsia, decreased visual acuity, and sudden-onset headache caused by pituitary adenoma complicated by apoplexy and abscess [31].

HRT was started in all patients, except for the child presenting with isolated hypoprolactinemia [31]. In 5 patients, all hormone deficiencies were substituted [23,27,28,32,33]. Information regarding HRT was incomplete in 2 studies [24,30]. Hypocortisolemia and diabetes insipidus were always corrected by HRT [23-30,32,33].

During follow-up, recovery of all affected pituitary axes was observed in one child [25]. Most authors reported persistent requirement of HRT after treatment of pituitary abscess, sometimes with partial recovery of pituitary function [24,26,28,29,32,33]. The follow-up period varied considerably between articles and often lasted several months, up to a maximum duration of 17 years [24-26,28,29,31-33]. Three studies did not report follow-up [23,27,30].

Other case studies

The remaining 14 cases are detailed in Table 1 and Supplementary Table 4 and involved children with active or a history of infection different from TBC and pituitary abscess [34-46]. Group B streptococcal meningitis was the most frequent infection in this group, affecting 4 children [35,36,38,46]. Hypopituitarism was suggested to be a sequela of infection in 4 patients, as it was diagnosed at least 1 year after the infectious disease: poliomyelitis

(1 case), group B streptococcal meningitis (2 cases), and viral meningitis (1 case) [34,36,38,39]. In the other 10 patients, hypopituitarism occurred during active infection or within the months after [35,37,40-46]. Various microorganisms were involved (see Table 1 and Supplementary Table 4). Among these patients, 7 exhibited features of severity such as hypotension, tachy- or bradycardia, hypotonia, altered consciousness, and/or seizures [35,40,43-46]. The pituitary-thyroid axis was found to be deficient in all 7 children. Well-documented thyroid-stimulating hormone (TSH) deficiency was present in 6 of them [40,43-46]. ACTH deficiency and/or low cortisol were also very frequent (6 cases) [35,40,43,44,46]. Six critical children suffered from meningitis, meningoencephalitis [35,40,45,46], or infection-associated encephalopathy [44].

Furthermore, we identified 2 studies that investigated pituitary function in children (19 and 12 patients below the age of 18 years) who had a history of infectious meningitis of different etiologies [47,48]. The time between the acute event and the hormonal evaluation varied from 3 months to 4.3 years. No pituitary hormone deficiencies were detected. At last, we included a study that retrospectively examined growth in 22 boys with HIV-infection (without overt acquired immunodeficiency syndrome) secondary to repeated transfusions with clotting factor concentrate for treatment of hemophilia [49]. Three boys had a growth velocity below <2 standard deviations for age, for more than 2 years after the onset of HIV-infection. However, assessment of pituitary activity did not reveal abnormalities of growth hormone, cortisol, or thyroxine levels.

Causative infection (number of cases)	**Patient characteristics**	**Deficient pituitary axes**	**Most frequent symptoms and other clinical features at time of diagnosis of hypopituitarism**	**Extent of endocrinological recovery**
TBC of the central nervous system (17): - Isolated TBM (8) [7-14] - Tuberculoma (7) [15-20] - Suprasellar abscess (1) [21] - Suspected TBC of the central nervous system (1) [22]	- 4 girls [13,18-20] - 13 boys [7-12,14-17,19,21,22] Median age 13 years (range 3-17)	- Somatotropic: 9 cases [9-13,15,20-22] - Adrenal: 8 cases [11,12,14,15,18,19,21] - Thyroid: 6 cases [7,11,18,19,21] - Gonadal: 7 cases [7-10,12,17,21] - Diabetes insipidus: 10 cases [8-10,12,13,15,16,19,21,22]	Isolated TBM: - History of TBM for which treatment months to several years earlier in all 8 cases [7-14] - Features of hypopituitarism in 7 cases [7-13], with an acute presentation in 2 children (central hypoadrenalism) [11,12] - No symptoms or clinical signs reported in 1 case [14] Tuberculoma: - Features of hypopituitarism in 5 cases [15-18,20] - Headache, emesis and/or visual disturbances in 4 cases (present for 1 week to several months, or duration not specified) [16,18,19] - Fever in 1 case [19]	- Persistent requirement of HRT: 4 cases [7,12,15,22] - Complete recovery of pituitary function: 2 cases [18,20] - Death: 3 cases [8,16,21] - No FU reported: 8 cases [9-11,13,14,17,19]

Pituitary abscess (12): - Primary abscess (8) [23,25-27,29,30,33] - Abscess secondary to Rathke's cleft cyst or adenoma (3) [24,31,32] - Pituitary abscess vs lymphocytic hypophysitis in a context of decapitated meningitis (1) [28]	- 9 girls [23-26,28-30,32,33] - 3 boys [26,27,31] Median age 15.5 years (range 8-17)	- Somatotropic: 4 cases [24,26,30] - Adrenal: 10 cases [23,24,26-30,32,33] - Thyroid: 11 cases [23-30,32,33] - Gonadal: 6 cases [24-26,29,30] - Diabetes insipidus: 9 cases [23-27,29,30,33]	- Features of hypopituitarism in 10 cases [23-27,29,30,32,33] - Headache of variable duration in 9 cases (present for several weeks or months in the majority of children) [23,25,26-29,31-33] - Acute presentation with features of additional meningitis, encephalitis, pressure on the optic chiasma and/or intracranial hypertension in 4 cases [28,29,31,33] - Fever in 1 case [33]	- Persistent requirement of HRT: 7 cases [24,26,28,29,32,33] - Persistent, not substituted hormone deficiency: 1 case (hypoprolactinemia) [31] - Complete recovery of pituitary function:1 case [25] - No FU reported: 3 cases [23,27,30]
Other infections (14): Viral: - Poliomyelitis (1) [34] - Perinatally acquired HIV-infection (1) [37] - Viral meningitis: unidentified virus (1) [39] - Nephropathia epidemica (Puumula hantavirus infection) (1) [41] - Influenza A-associated encephalopathy (2) [44] - Viral Human Parechovirus encephalitis (1) [45] Bacterial: - Group B streptococcal meningitis (4) [35,36,38,46] - Salmonella enteriditis sepsis (1) [43] - Acute granulomatous Acanthamoeba encephalitis (1) [40] - Blastomycosis of the central nervous system (1) [42]	- 7 girls [36-38,41,43-45] - 7 boys [34,35,39,40,42,44,46] Median age 6 years (range 9 days - 17 years)	- Somatotropic: 5 cases [35-38,42] - Adrenal: 9 cases [35,38-40,42-44,46] - Thyroid: 10 cases [34,35,38,40,42-46] - Gonadal: 4 cases [38,40-42] - Diabetes insipidus: 6 cases [35,38,42,44,46]	- No current but a history of infection (>1 year earlier) in 4 cases (group B streptococcal meningitis: 2 cases; poliomyelitis: 1 case; viral meningitis with unidentified virus: 1 case) [34,36,38,39] - Features of hypopituitarism in 11 cases (including hemodynamic instability, although not discernable from sepsis) [34-38,42-46] - Features of severity in 7 children (hypotension, tachy- or bradycardia, hypotonia, altered consciousness, and/or seizures), during active infection or within the months after [35,40,43-46] - One child with a history of group B streptococcal meningitis was declared dead at initial presentation [38]	Current or recent infection (<1 year): - Persistent hypopituitarism +/- HRT: 2 cases [41,42] - Complete recovery of pituitary function: 1 case [45] - Death: 3 cases [43,44] - No or insufficient data reported: 4 cases [35,37,40,46] History of infection (>1 year earlier): - Death (declared at initial presentation): 1 case [38] - No FU reported: 3 cases [34,36,39]

Table 1: Summarizing table of the infectious causes of hypopituitarism in children; HRT: hormonal replacement therapy; FU: follow-up; TBC: tuberculosis; TBM: tuberculous meningitis.

Discussion

In this systematic review, we synthesize the evidence on infectious causes of pediatric hypopituitarism published in literature. Infection is a known cause of hypopituitarism in children as cases have since long been presented. Currently, scarce evidence about this topic is available for clinicians in forms different from case studies. This review outlines which infections may be involved when hypopituitarism is detected in a child. Similarly, it provides an overview of the infectious conditions in which the potential risk of pituitary disturbances must be considered.

Children with hypopituitarism due to infection display variable clinical manifestations dependent on the affected hormonal axes and the causative infectious disease. Pituitary abscess and TBC of the central nervous system were the most frequently reported infectious etiologies of pediatric hypopituitarism [7-33]. In both abscess and TBC, anterior pituitary insufficiency often was symptomatic [7-13,15-18,20,21,23-27,29,30,32,33]. Concomitant headache can be suggestive of a (supra-)sellar abscess or tuberculoma [16,18,19,21,23,25,26-29,31-33], and additional features of intracranial hypertension, pressure on the optic chiasma, meningitis, or encephalitis [16,18,19,27-29,31,33], should expedite diagnostic investigations. On the other hand, isolated pituitary insufficiency, without headache or other non-endocrinological features, should prompt physicians to inquire a history of TBM [7-14].

Vital organ functions can be compromised, especially in children with active viral, bacterial, or even amebic meningitis or meningoencephalitis [35,40,45,46]. In acute meningitis or meningoencephalitis with coexistent hypopituitarism, hemodynamic instability can be attributed to sepsis, as well as to pituitary dysfunction [35,46]. Indeed, we found that the pituitary-adrenal and -thyroid axes were the most often disturbed hormonal axes during infection associated with circulatory collapse [35,43,44,46].

Our results demonstrated fever to be present in a minority of children who have pituitary abscess [33], and this finding is consistent with data from non-pediatric case series [30,31]. Furthermore, cultures were negative in a substantial proportion of cases [24,27,28,30,33]. Possible explanations are inadequate technique for bacteria isolation or early antibiotic therapy initiated before taking samples for culture [31]. Some authors have proposed that in a context of negative microbiology, these lesions may correspond to an aseptic, liquefactive necrosis of the pituitary gland or a pituitary tumor, or the content of a Rathke's cleft cyst [26]. Consequently, it remains unclear whether we should consider culture-negative cases to be pituitary abscesses [30].

Although follow-up was not described in many primary studies and duration of follow-up was variable, we found that long-term morbidity is considerable as complete recovery of pituitary function was rarely seen [18,20,25,45], and HRT often persistently required [7,12,15,22,24,26,28,29,32,33,42]. Death is not uncommon and may directly result from or be related to hypoadrenalism and/or hypothyroidism [16,21,43,44].

To ensure a correct interpretation of our results, it is important to note that alterations of the hypothalamic-pituitary-peripheral hormone axes occur in systemic diseases, such as any critical illness, as an adaptive response to stress [50]. During an acute stressful event, ACTH, growth hormone, and prolactin levels increase. TSH, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) generally either decrease or remain unchanged, along with a reduced activity of corresponding target organs. In prolonged critical illness, there is a uniform decrease in secretion of all anterior pituitary hormones. A well-described entity is the non- thyroidal illness syndrome that corresponds to a transient suppression of the hypothalamic-pituitary-thyroidal axis in conditions such as bacterial sepsis or septic shock, chronic malnutrition, surgery and probably any severe illness [45,50,51]. This adaptive pituitary response to stress may in part explain the occurrence of hypopituitarism in children with infectious diseases, specifically in children with sepsis, and even more so in the absence of a pituitary lesion on brain imaging.

This systematic review has several limitations. First, we may not have included all relevant articles, since we did exclusively request unavailable full texts from KU Leuven Library when title and abstract met the inclusion criteria, as explained previously. However, we esteem that the studies we included represent the major infections associated with pediatric hypopituitarism and published in literature. Second, in the absence of higher-level evidence, we only included case reports and series. We may therefore over- or underestimate the relative importance of some infectious etiologies of anterior pituitary insufficiency in childhood. Particularly, we believe hypopituitarism in children with sepsis to be underreported.

Furthermore, we noted a lack of accuracy in the way hormone deficiencies were established among some of the primary studies [15,19,22,23]. We attempted to limit resultant bias through critical appraisal of which endocrinopathies to withhold in this review. However, another concern is that several studies did not report the patients' hormonal values and neither specified the cut-off levels used in biological tests to define the different hormone deficiencies [8,16,17,24,26,30,40]. We decided to still use their data since symptoms and clinical signs were compatible with hypopituitarism and/or the patient's underlying medical condition

made hypopituitarism plausible. Our decision to include these articles was also motivated by the rarity of the matter discussed in this systematic review.

Finally, hormonal tests performed in the oldest studies sometimes differed from those used in current practice [7,9,34]. Consequently, we assessed the validity of described hormonal deficits with specific attention to the child's clinical presentation. Indeed, these older case studies generally provided detailed clinical descriptions [7,9]. Nevertheless, the lack of quantitative data we tolerated in a significant proportion of primary studies because of scarce available literature, as well as diagnostic heterogeneity between studies, are important limitations of this review.

Our work opens several future research directions. As demonstrated above, TBC of the central nervous system and pituitary abscess have been most frequently associated with pediatric hypopituitarism in literature [7-33]. However, the occurrence of anterior pituitary insufficiency in septic children needs to be further explored. Only a few previous studies investigated the incidence of pediatric hypopituitarism following infectious diseases, and mainly in meningitis [47-49]. To better understand the incidence and outcome of hypopituitarism in the infections we discuss, prospective studies in sufficiently large study populations are required. These could enable to establish whether endocrinological screening and follow-up are recommended.

Conclusion

In conclusion, the main infectious etiologies of pediatric hypopituitarism documented so far are TBC and pituitary abscess [7-33], along with meningitis and meningoencephalitis caused by different microorganisms [34-46]. There is marked heterogeneity in symptoms and clinical signs among patients, that are determined by the affected pituitary axes and the causative infectious disease. Failure of hemodynamic homeostasis is possible and may be explained by anterior pituitary insufficiency and systemic responses to infection [12,35,43,44,46]. Mortality and long-term morbidity are considerable [7,8,12,15,16,21,22,24,26,28,29,32,33,38,42-44], and make raising awareness among physicians necessary. There is a need for future pediatric research to evaluate the incidence and evolution of pituitary dysfunction in the infections reviewed in this work. It may be most valuable to start with an initial focus on hypopituitarism in sepsis.

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Ethical Approval

This systematic review was ethically approved by KU Leuven.

Conflict of Interest: None.

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