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HORMONAL IMBALANCES: CAUSES, SYMPTOMS, AND TREATMENT-AN UPDATED REVIEW

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ABSTRACT

Background: The nervous and endocrine systems are crucial for maintaining homeostasis, and disruptions in endocrine function can lead to various neurologic symptoms. These manifestations can provide insights into endocrine disorders affecting pediatric patients, allowing for comprehensive diagnosis and management. **Aim:** This review aims to summarize the neurologic manifestations associated with different endocrine disorders and their implications for diagnosis and treatment in children. **Methods:** The article discusses various neurologic symptoms linked to endocrine disorders, including headaches, altered mental states, muscle abnormalities, and developmental issues. It examines the role of the hypothalamic-pituitary system in regulating hormone secretion and maintaining homeostasis. A detailed exploration of specific neurologic symptoms, such as idiopathic intracranial hypertension (IIH) and its connection to endocrine dysfunction, is included. **Results:** Common neurologic manifestations include headaches, altered mental status, muscle weakness, cramps, and developmental delays. The review highlights how conditions like hyperthyroidism, hypothyroidism, adrenal disorders, and growth hormone deficiencies contribute to these symptoms. Endocrine disorders can lead to significant cognitive and behavioral changes in children, underscoring the importance of early detection and intervention. **Conclusion:** This updated review emphasizes the complex interplay between endocrine and neurologic systems, particularly in pediatric populations. Recognizing neurologic symptoms associated with endocrine disorders is critical for timely diagnosis and treatment, ultimately improving patient outcomes.

KEYWORDS: endocrine disorders, pediatric patients, neurologic manifestations, hypothalamic-pituitary system, homeostasis, cognitive function.

INTRODUCTION

Both the nervous and endocrine systems play integral roles in maintaining homeostasis. Consequently, disruptions in endocrine function may lead to various neurologic symptoms that can manifest in a range of endocrine disorders, including those affecting the pituitary, thyroid, parathyroids, pancreas, adrenal glands, and gonads. Recognizing these neurologic signs and symptoms is advantageous for both the diagnosis and management of endocrine disorders, helping clinicians to address these conditions comprehensively. This article offers a summary of neurologic manifestations associated with different endocrine disorders affecting pediatric patients. Initially, the article details various neurologic symptoms that may occur in these disorders, specifying each symptom alongside its potential endocrine source. Additionally, the article discusses neurologic findings either related to the endocrine disorders or resulting from their management approaches.

Hypothalamic-pituitary system: An understanding of the hypothalamic-pituitary system is essential, given its critical role in linking the nervous and endocrine systems. The neuroendocrine system, comprising both systems, collaborates to ensure consistent bodily functions. This relationship focuses on how the hypothalamus regulates pituitary hormone secretion, but it also encompasses complex reciprocal interactions between the two systems to preserve homeostasis and enable appropriate responses to external stimuli via controlled secretion of hormones, neurotransmitters, or neuromodulators.[1,2] Neurons release neurotransmitters and neuromodulators at synaptic junctions, while neurosecretory cells discharge substances directly into the bloodstream, where they function as hormones,

including neurohypophyseal and hypophysiotropic cells. The hypothalamus stands as the central brain structure for homeostasis, housing numerous specialized nuclei that receive sensory data from both the external and internal environments—such as light, pain perception, temperature, blood pressure, blood osmolality, and glucose levels.[1,2] Several hormones also provide direct negative or positive feedback to the hypothalamus. Through coordinated signaling with the pituitary glands, cerebral cortex, brainstem, spinal cord, and sympathetic and parasympathetic preganglionic neurons, the hypothalamus orchestrates homeostasis via synchronized endocrine, behavioral, and autonomic responses.[1,2]

Specific Neurologic Manifestations in Endocrine Disorders

Endocrine dysfunctions can produce various neurologic signs and symptoms, including headache, altered mental state, changes in muscle strength and tone, muscle stiffness and cramps, movement abnormalities, and psychomotor delays.[3]

Headache: Headache, although often nonspecific, may be linked to underlying pathological conditions, such as idiopathic intracranial hypertension (IIH).[3] IIH, or pseudotumor cerebri syndrome (PTCS), refers to elevated intracranial pressure despite normal brain tissue and cerebrospinal fluid (CSF) composition.[4] Common symptoms include headache, vomiting, visual disturbances, abducens nerve palsy, and papilledema, with irritability, drowsiness, or apathy in younger children.[3] Untreated cases can lead to optic atrophy and rapid vision loss, underscoring the need for timely diagnosis and intervention. The precise cause of PTCS remains uncertain but has been associated with endocrine dysfunctions like adrenal insufficiency, diabetic ketoacidosis during treatment, hypoadrenalism, hyperthyroidism, and hypoparathyroidism.[3] Sheldon et al.[4] described pediatric PTCS as a neuroendocrine disorder involving hormonal and metabolic imbalances across the hypothalamic-pituitary-adrenal axis, renin-angiotensin-aldosterone system, growth hormone, insulin-like growth factor-1 (IGF-1), hypothalamic-pituitary-thyroid axis, hypothalamic-pituitary-gonadal axis, and posterior pituitary-antidiuretic hormone regulation.

Altered Mental Status: Altered mental status is a frequent presentation in emergency settings and may indicate endocrine emergencies.[5] Maintenance of attention, awareness, and consciousness requires coordination among the brainstem reticular formation, thalamus, and cerebral cortex.[6] Impaired consciousness reflects a substantial change in wakefulness and environmental awareness.[7] Identifying underlying causes and stabilizing vital signs promptly is critical.[5,8] Altered mental status in children may result from infectious, inflammatory, structural, metabolic, toxic, or nutritional origins.[8] Metabolic or endocrine encephalopathy is a differential diagnosis in cases without focal neurological signs or meningeal irritation.[8] In emergency contexts, diabetic coma is considered, particularly from diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic syndrome.[9,11] Hypoglycemia or cerebral edema post-DKA treatment may also cause symptoms ranging from general weakness and lethargy to coma.[8] Adrenal crises in conditions such as congenital adrenal hyperplasia, adrenal hypoplasia, familial glucocorticoid deficiency, or ACTH deficiency can lead to mental status alterations.[8] Similarly, hypocalcemic tetany or seizure due to hypoparathyroidism may impair consciousness.[3] Increased serum calcium, exceeding 11 mg/dL, may result in symptoms like apathy, delirium, or psychosis.[3] Thus, initial evaluations for altered mental status should include blood glucose, calcium, and electrolyte levels. Severe hyperthyroidism or hypothyroidism can infrequently cause altered mental states, such as thyroid storm or myxedema coma, which may be fatal if untreated.[12] Symptoms can include behavioral and cognitive changes, seizures, psychosis, involuntary movements, and even coma. In myxedema coma, historical thyroid disease and symptoms such as lethargy, hypothermia, bradycardia, constipation, dyspnea, yellowed and dry skin, and macroglossia may be observed, occasionally accompanied by seizures. Thyroid storm, on the other hand, may present fever, tachyarrhythmias, tachypnea, dyspnea, heart failure, gastrointestinal symptoms, tremors, anxiety, and confusion, potentially advancing to coma. Triggering factors include major surgery, trauma, systemic infections, severe emotional stress, or DKA. As such, thyroid function should be assessed in DKA management. A case report of thyroid storm as cardiorespiratory distress in a two-year-old referred for urgent lung perfusion imaging highlights the importance of considering thyroid disease in unstable patients.[13] Additionally, Hashimoto's encephalopathy, linked to autoimmune thyroid conditions, manifests as a steroid-responsive encephalopathy with antithyroid antibodies present.[14,16]

Muscle Problems: Abnormalities in muscle strength, tone, and gait can often signify underlying endocrine disorders, where symptoms such as muscle weakness, pain, and stiffness are commonly observed.[3] Typically, distinctive systemic symptoms related to specific endocrine disorders appear before muscle weakness; however, in some cases, muscle weakness may be the initial indication.[3] It is important to consider endocrine myopathy as a possible cause, as specific treatments are available for this condition.[17] Endocrine-related myopathies can arise from thyroid disorders (hyperthyroidism or hypothyroidism), parathyroid abnormalities (hyperparathyroidism or hypoparathyroidism), and adrenal disorders (e.g., Cushing's disease, Addison's disease, or hyperaldosteronism).[3,17,18] According to Kruse[18], childhood endocrine myopathies typically involve proximal muscles, such as those in the pelvic or shoulder

girdle, with mild morphological changes in muscle tissue despite severe symptoms, and these myopathies generally respond well to treatment. Muscle weakness is often more pronounced in the lower limbs than the upper limbs, and gait abnormalities may be an early symptom of both proximal and distal lower limb weakness.[3] A case of subclinical hypothyroidism presenting as gait abnormality in an elderly man has been documented.[19] Furthermore, electrolyte imbalances, including hyper/hyponatremia, hyper/hypokalemia, hypophosphatemia, hypocalcemia, and hypomagnesemia, are recognized contributors to myopathies in endocrine disorders.[3,17] While deep tendon reflexes may be diminished, they are generally not absent, and serum creatine kinase levels typically remain within the normal range, although elevated levels do not necessarily correlate with the severity of weakness.[3]

Cramps, which are involuntary and painful muscle contractions, may occur under normal conditions, such as after intense exercise, but can also result from endocrine abnormalities, including adrenal insufficiency or thyroid dysfunction.[3] Stiffness and spasms, observed in myotonia and dystonia, may also appear in hypothyroidism or hyperthyroidism, where motor unit activity remains continuous.[3] Hypothyroid-associated stiffness may worsen with activity and can be painful, with slowed muscle contraction and relaxation evident during tendon reflex tests. Muscle tone, defined by resistance to passive movement, may decrease, indicating hypotonia.[3] Profound hypotonia associated with obesity and intellectual disability might suggest Prader-Willi syndrome (PWS), in which hypothyroidism is a significant endocrine condition linked to hypotonia.[20,21] Webb et al.[22] described neuromuscular dysfunction in adults with growth hormone deficiency (GHD), who experienced fatigue, tiredness, and myalgia, as evidenced through muscle biopsies and neurophysiological studies. Schweizer et al.[23] noted that high doses of growth hormone treatment for short-statured children born small for gestational age (SGA) improved height, muscle mass, and function, along with a reduction in fat mass. Additionally, Reus et al.[24] reported that GH therapy in infants with PWS increased muscle thickness, which correlated with enhanced muscle strength and motor development. Movement disorders, characterized by involuntary movements like chorea, athetosis, and tremors, can also stem from endocrine conditions.[3] Chorea, characterized by rapid, repetitive, non-rhythmic movements, has been associated with hyperthyroidism.[3] Athetosis, involving slow, writhing limb movements, frequently accompanies chorea and can occur in cases of hyperthyroidism, Addison's disease, hypernatremia, hypocalcemia, and hypoparathyroidism.[3,37] Tremors, rhythmic oscillations, may occur physiologically but can also suggest hyperthyroidism as a causative factor.[3]

Development Problems: Endocrine abnormalities can impact developmental progression. Studies investigating growth hormone deficiency (GHD) have shown its effects on brain structure, motor function, and cognition through assessments and MRI scans in children with GHD, revealing lower cognitive scores, white matter changes in the corpus callosum and corticospinal tract, and reduced thalamic, hippocampal, and globus pallidus volumes compared to controls with idiopathic short stature.[25] In a study of thirty Korean patients with PWS, more than two years of growth hormone treatment in 14 infants and toddlers led to an increase in head circumference, IGF-1 levels, IGF binding protein-3 levels, lean body mass, and bone mineral content, alongside improvements in motor development.[26] Thyroid hormones play a vital role in neuronal migration, differentiation, and myelination, including cerebellar development.[27] In transgenic mouse models, thyroid dysgenesis or reduced thyroid hormone levels in brain tissue were linked to cerebellar abnormalities such as ataxia, poor balance, coordination deficits, and decreased locomotor activity.[27] Congenital hypothyroidism, stemming from thyroid dysgenesis or dyshormonogenesis and occurring in approximately 1 per 3,000-4,000 live births, may lead to developmental delays if left untreated. Early detection and thyroid hormone replacement therapy are essential for optimal outcomes. The neonatal screening program in Korea facilitates early diagnosis and intervention for almost all cases of congenital hypothyroidism during the newborn period. For cases of floppy male infants with developmental delays, particularly those without a history of perinatal asphyxia, it is advantageous to consider genetic causes such as MCT8 mutations (Allan-Herndon-Dudley syndrome).[21,28] Rodrigues et al.[21] underscored that simple assessments of triiodothyronine, thyroxine, and thyroid-stimulating hormone levels can guide diagnosis, circumventing numerous invasive and costly tests, and enabling appropriate genetic counseling for families.

Recent studies have highlighted the association between various adrenal disorders and neurological symptoms.[29,32] For instance, cognitive and behavioral abnormalities have been observed in children with Cushing syndrome, even after recovery from hypercortisolism.[29] Excessive glucocorticoid replacement during treatment for adrenal insufficiency in children has been linked to neurological and MRI findings such as delayed myelination and brain atrophy.[29] Although clinical implications remain uncertain, reports suggest that patients with congenital adrenal hyperplasia (CAH) are predisposed to white matter abnormalities, temporal lobe atrophy, or hippocampal dysgenesis, potentially as a result of the disease and its treatment. Symptoms like intellectual disability, tremor, asymmetric tendon reflexes, and cerebellar dysfunction have been documented in some patients with CAH.[30,31] Ghetti et al.[33] demonstrated that children with a history of diabetic ketoacidosis

(DKA) exhibited significantly lower accuracy in memory tasks related to color and spatial functions compared to those without a DKA history, concluding that DKA impairs memory function and emphasizes the importance of DKA prevention.

Neurological features associated with specific endocrine disorders

Hypothalamic-Pituitary Dysfunction: Prompt diagnosis of hypothalamic-pituitary lesions is crucial. Endocrine symptoms frequently precede neuro-ophthalmic signs. In a retrospective cohort study involving 176 pediatric patients (median age 6 years, range 0.2–18 years) with hypothalamic-pituitary lesions, including craniopharyngioma, optic pathway glioma, suprasellar arachnoid cyst, hamartoma, germ cell tumor, and hypothalamic-pituitary astrocytoma, two-thirds exhibited abnormal BMI or reduced growth velocity prior to neuro-ophthalmic symptoms.[34] This finding highlights the need for a proactive approach to diagnosing hypothalamic-pituitary lesions by investigating endocrine symptoms early.[34] After traumatic brain injury in children, acute endocrine alterations, including changes in the hypothalamic-pituitary-adrenal axis and fluctuations in antidiuretic hormone production, are common.[35,36] Long-term effects may include both transient and lasting pituitary dysfunctions, such as growth hormone deficiency, pubertal disorders, ACTH deficiency, diabetes insipidus, central hypothyroidism, and hyperprolactinemia. Routine monitoring for at least a year post-injury is recommended to promptly identify hormonal imbalances and support normal growth and development.[35]

Thyroid Disorders: Congenital hypothyroidism can present with symptoms like intellectual disability, hypotonia, constipation, somnolence, apnea, large fontanelles, and sensorineural hearing loss.[17,37] It may also be associated with Kocher-Debre-Semelaigne syndrome, characterized by generalized muscle hypertrophy, particularly in the calf muscles, and linked to hypothyroidism.[38] In infancy and childhood, hypothyroid myopathy often presents with muscular hypertrophy, myxedema, and short stature. While congenital hypothyroidism is detectable in neonates through screening, rare cases may be missed, necessitating repeat thyroid function tests if clinical symptoms indicative of hypothyroidism emerge. Neonatal hyperthyroidism may result in craniosynostosis and developmental delays. Acquired hypothyroidism may be accompanied by symptoms such as psychosis, seizures, ataxia, and coma.[12,37] Hashimoto's encephalopathy, an immune-mediated condition associated with hypothyroidism, may result in cerebral hypoperfusion due to vasculitis. Although rare in children, it typically responds well to steroid or immunotherapy, leading to favorable outcomes.[14,16] Graves' disease can manifest neurological symptoms such as emotional instability, anxiety, irritability, restlessness, and inattentiveness. Neuromuscular symptoms, including muscle weakness or cramps, as well as ocular issues like lid lag, convergence impairment, or ophthalmoplegia, are also reported. Movement disorders, including tremor or chorea, may develop, while thyrotoxic periodic paralysis or myasthenia gravis is rare in hyperthyroidism.[17,37] Severe thyrotoxicosis may progress to alter consciousness in cases of thyroid storm.[12]

Parathyroid Disorders: Neurological symptoms associated with parathyroid disorders are linked to serum calcium concentrations. Hypoparathyroidism can lead to hypocalcemia, resulting in muscular discomfort, cramps, numbness, rigidity, tetany, apnea, and seizures. Additionally, elevated intracranial pressure may present with headaches and vomiting.[17,37,39] Autoimmune polyendocrine syndrome type 1 (APS1) was documented in two siblings who experienced hypocalcemic seizures followed by hypoparathyroidism.[40] Conversely, hyperparathyroidism can induce hypercalcemia, which may cause muscle weakness, loss of appetite, nausea, vomiting, and encephalopathy.[17,37,39] Other symptoms may include excessive thirst, increased urination, weight loss, headaches, seizures, and psychiatric manifestations.[17,37,39] Although primary hyperparathyroidism is uncommon in pediatric populations, severe central nervous system and metabolic disturbances can occur. Therefore, it is crucial to interpret hypercalcemia cautiously and ensure prompt diagnosis to prevent complications.[41]

Adrenal Disorders: Primary adrenal insufficiency encompasses conditions such as congenital adrenal hyperplasia (CAH), autoimmune polyglandular syndrome (APS), ACTH resistance, adrenoleukodystrophy, adrenal hypoplasia congenita, adrenal hemorrhage, and the IMAGe syndrome (characterized by intrauterine growth restriction, metaphyseal dysplasia, adrenal hypoplasia congenita, and genital anomalies).[42,43] Manifestations of this condition may include hypotension, hyperpigmentation, hyponatremia, hyperkalemia, and hypoglycemia. Notably, hyperkalemia may be absent in childhood cases of primary adrenal insufficiency, indicating that its absence does not exclude this diagnosis.[42] The suspicion of adrenal insufficiency should arise in patients presenting with a combination of chronic or subacute symptoms, including persistent fatigue, muscular weakness, anorexia, nausea, vomiting, diarrhea, hypotension, weight loss, headaches, and skin hyperpigmentation.[42,44] Initial evaluations for suspected primary adrenal insufficiency may include serum ACTH, aldosterone, or plasma renin activity assessments. Both absolute and relative adrenal insufficiency can develop in critically ill children experiencing systemic inflammatory response syndrome or sepsis.[45,47] In scenarios involving catecholamine-resistant shock, it is vital to investigate potential adrenal insufficiency, with the ACTH stimulation test serving as a useful diagnostic tool.[44,46] Excessive glucocorticoid levels in primary or secondary

Cushing syndrome may manifest as headaches, proximal muscle weakness, cognitive impairments, and behavioral disturbances.[3,17,29] Hypokalemia-induced weakness can occur in hyperaldosteronism, necessitating the inclusion of primary aldosteronism and pheochromocytoma in differential diagnoses for hypertension.[17]

Diabetes Mellitus: Diabetic ketoacidosis (DKA) and cerebral edema can present with various neurological symptoms.[48,49] Signs such as agitation, confusion, lethargy, headaches, and vomiting may accompany cerebral edema. To prevent cerebral edema, a gradual rehydration process over 48 hours, avoidance of hypotonic fluids, cautious bicarbonate use, and careful hyperglycemia management are recommended. If cerebral edema is suspected, immediate interventions such as rapid mannitol infusion, head elevation, fluid restriction, and hyperventilation should be initiated. Hypoglycemia can also lead to numerous neurological symptoms, including tremors, confusion, behavioral changes, blurred vision, seizures, and coma. Although cerebral edema is a common cause of neurological decline in children with DKA, there is also a risk of stroke due to hyperglycemia and DKA increasing susceptibility to thrombosis.[50] Therefore, it is prudent to consider the potential for thrombosis, infection, or hemorrhage when focal neurological deficits or deteriorating conditions arise in DKA patients.[50,51] While symptomatic diabetic neuropathy (DNP) is rare in children, subclinical DNP is prevalent among children and adolescents with at least five years of type 1 diabetes mellitus.[52] Despite the infrequency of clinical DNP in younger populations, neurophysiological studies can identify its presence.

CONCLUSION

In conclusion, the interconnection between the nervous and endocrine systems plays a vital role in maintaining homeostasis, particularly in pediatric populations. The review elucidates the diverse neurologic manifestations that can arise from various endocrine disorders, emphasizing the importance of recognizing these symptoms for effective diagnosis and management. Neurologic symptoms such as headaches, altered mental states, and muscle abnormalities serve as critical indicators of underlying endocrine dysfunctions. For instance, conditions like idiopathic intracranial hypertension (IIH) highlight the potential complications of untreated endocrine disorders, leading to severe outcomes such as vision loss. Furthermore, altered mental status can signal endocrine emergencies, necessitating prompt evaluation and intervention to stabilize pediatric patients. The review also underscores the impact of growth hormone deficiencies and thyroid disorders on cognitive and developmental trajectories, suggesting that timely identification and treatment can mitigate long-term repercussions. Additionally, it is crucial to consider the potential cognitive and behavioral changes associated with adrenal disorders, as evidenced by the neurodevelopmental implications observed in conditions like Cushing syndrome and congenital adrenal hyperplasia (CAH). The findings presented in this review advocate for a multidisciplinary approach to patient care, integrating endocrinology and neurology to ensure comprehensive assessment and management strategies. Ultimately, increased awareness and understanding of the neurologic manifestations of endocrine disorders will enable healthcare professionals to provide more effective care for pediatric patients, thereby improving overall health outcomes and quality of life. Further research is necessary to explore the long-term effects of endocrine imbalances on neurologic development and function, guiding future therapeutic interventions and improving the standard of care for affected children.

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اختلالات هرمونية: الأسباب، الأعراض، والعلاج ـ مراجعة محدثة

الملخص :الخلفية :تعتبر الأنظمة العصبية والغدد الصماء حيوية للحفاظ على التوازن الداخلي، ويمكن أن تؤدي الاضطرابات في وظيفة الغدد الصماء إلى ظهور أعراض عصبية متنوعة. يمكن أن توفر هذه المظاهر رؤى حول الاضطرابات الغدد الصماء التي تؤثر على المرضى الأطفال، مما يسمح بالتشخيص والإدارة الشاملة.

الهدف :تهدف هذه المراجعة إلى تلخيص المظاهر العصبية المرتبطة بمختلف الاضطرابات الغدد الصماء وتأثيراتها على التشخيص والعلاج لدى الأطفال.

الأساليب :يناقش المقال أعراض عصبية متنوعة مرتبطة بالاضطرابات الغدد الصماء، بما في ذلك الصداع، وتغيرات في الحالة العقلية، واضطرابات العضلات، ومشاكل في النمو. كما يستعرض دور نظام الهيبوثالاموس والغدة النخامية في تنظيم إفراز الهرمونات والحفاظ على التوازن الداخلي. يتضمن استكشافًا مفصلاً لأعراض عصبية محددة، مثل ارتفاع ضغط الدم داخل الجمجمة مجهول السبب (IIH) وارتباطه بخلل الغدد الصماء.

النتائج :تشمل المظاهر العصبية الشائعة الصداع، وتغيرات في الحالة العقلية، وضعف العضلات، والتشنجات، وتأخر النمو. تسلط المراجعة الضوء على كيفية مساهمة حالات مثل فرط نشاط الغدة الدرقية، ونقص نشاط الغدة الدرقية، واضطرابات الغدة الكظرية، ونقص هرمون النمو في هذه الأعراض. يمكن أن تؤدي الاضطرابات الغدد الصماء إلى تغييرات كبيرة في الوظائف الإدراكية والسلوكية لدى الأطفال، مما يبرز أهمية الكشف المبكر والتدخل.

الخاتمة :تؤكد هذه المراجعة المحدثة على التفاعل المعقد بين الأنظمة الغدد الصماء والعصبية، وخاصة في الفئات السكانية الأطفال. إن التعرف على الأعراض العصبية المرتبطة بالاضطرابات الغدد الصماء أمر حيوي للتشخيص والعلاج في الوقت المناسب، مما يؤدي في النهاية إلى تحسين نتائج المرضى.

الكلمات المفتاحية :الاضطرابات الغدد الصماء، المرضى الأطفال، المظاهر العصبية، نظام الهيبوثالاموس والغدة النخامية، التوازن الداخلي، الوظيفة الإدراكية.