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Article/Review

Complex diagnostics and prognostic aspects of neuro-endocrinological indicators in combined acute traumatic brain injuries

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Abstract: Combined acute traumatic cerebral injury causes direct damage to brain structures and disrupts the work of distant organs, depending on the severity of the traumatic factor. Neuroendocrine disorders are often underdiagnosed in combined acute traumatic brain injuries, which entails the development of complications in both the acute and chronic phases of the disease. The purpose of this study was to analyse the latest scientific evidence on neuro-endocrinological indicators in combined acute traumatic brain injuries to improve patient management protocols and overall survival rates. The research papers from open databases over the past five years have been analysed. It was found that the most common neuro-endocrinological conditions after brain injuries are hypopituitarism, diabetes insipidus, hypothalamus dysfunction, and cognitive disorders. Low blood pressure (both systemic and internal cerebral), anaemia and hypoxia can cause ischemic changes in the central endocrine glands. In the acute phase of the course of combined traumatic brain injuries, signs of deficiency of somatotropic, gonadotropic, and adrenocorticotropic hormones prevail. Vasopressin deficiency in the acute phase is associated with an increased risk of brain oedema, and oxytocin – with the development of neurodegenerative pathologies. Differential diagnosis of neuro-endocrine disorders should be carried out on the basis of anamnestic data and indicators of biochemical and hormonal data of the patient. The obtained data emphasise the importance of timely diagnosis of neuroendocrine disorders along with neurological disorders during the management of patients with traumatic brain injuries can be used both at the stage of primary diagnosis and during the rehabilitation process.

Keyword: adenohypophysis, trauma, central nervous system, neurological disorders, hypothalamus.

Quoting: Kahramonjon Kuldashev, Feruza Khaydarova, Yayraxon Kuldasheva, Zilola Khakimova, Gulmira Inomova. Complex diagnostics and prognostic aspects of neuro-endocrinological indicators in combined acute traumatic brain injuries. **2026**, 5, 1, 6. https://doi.org/10.56121/MSU-2026-1-00006

Received: 26.12.2025
Corrected: 16.01.2026
Accepted: 14.02.2026
Published: 27.02.2026

Introduction

Traumatic brain injury (TBI) is defined in internal medicine and neurology as the disturbance of brain structures due to negative (often mechanical) environmental influences of varying degrees of intensity [1]. According to the statistical data by T. A. Fatuki et al., every year almost three million people in the United States are hospitalised with traumatic brain injury, the cause of which is most often falls from a height, blows of various nature on the skull, and traffic accidents [2]. Retrospective studies show that less than 80% of hospitalised patients with TBI have a number of neurological, subjective symptoms on the part of the visual organ and vestibular apparatus, while the hormonal background of patients with acute TBI clinic at the initial stages is not considered [3]. Often the inconsistency of the methods used to diagnose the state of functional activity of organs (functional and visualising) leads to underdiagnosis and insufficient understanding of the possible mechanisms of damage to the central nervous system (CNS), which determines the relevance of the additional study of this problem.

Combined acute brain injuries annually affect more than ten million patients worldwide and more than one and a half million people annually in the United States [[4]. The number of cases of mild TBI, most often due to traffic accidents, is gradually increasing in low- and middle-income countries [5]. According to the published statistics of the Republic of Uzbekistan, acute TBI is diagnosed in every sixth person throughout life, while the total number of TBI cases per year exceeds 40 million [6]. Moreover, 15% of patients with combined TBI have complications in the form of disability, and 10% have a fatal outcome [7]. Statistical data by K. E. Makhkamov et al. indicate that on average they supervise more than 5 thousand patients with acute TBI per year and more than 30 thousand surgical interventions from this occasion to the central nervous system [8]. This means that adequate diagnosis of combined acute TBI is an urgent issue in the field of emergency medicine and neurology all over the world.

Clinical symptoms, including a complex of neurological and endocrine signs, occur more often in the form of isolated neurological symptoms during the treatment of TBI and require both general clinical and special imaging diagnostic methods [9]. Combined syndromes, which are detected in the post-traumatic period of TBI, lead to a significant decrease in the quality of life of patients and a deterioration in the dynamics of rehabilitation [10]. According to F. T. Mahmudova et al., almost a quarter of patients with TBI in Uzbekistan require emergency psychiatric care in the acute phase of the illness [11]. Thus, the complex manifestations of TBI, including central endocrine and peripheral hormonal disturbances, as opposed to purely neurological, worsen treatment outcomes and symptomatic outcome for the patient.

In addition to the negative impact on the patient's quality of life and objective clinical indicators in the long-term period of the disease, neuroendocrine disorders are constituent elements in the pathogenesis of the development of early complications of TBI, according to C. Mahajan et al. [12]. Among the critical neuroendocrine conditions in brain injury, hypopituitarism stands out, which often leads to a number of systemic complications [13]. Hypopituitarism in patients with acute TBI is dangerous by affecting the peripheral organs of the endocrine system, which, in turn, complicates the management and control of post-traumatic conditions not only in the acute phase, but also in the long-term management of the patient. According to Yu. M. Urmanova and D. I. Khamraeva, among the neuroendocrine complications of patients with acute TBI in Uzbekistan, diabetes insipidus (DI) is often diagnosed, which requires constant monitoring in the long-term period of the disease, significantly affecting the quality of rehabilitation of patients [14].

Thus, the purpose of this study was to analyse the main nosological forms of neuroendocrine disorders and their pathophysiological mechanisms that occur in patients with combined acute brain injuries to improve comprehensive diagnostic protocols and patient management with a focus on reducing the risks of complications at different stages of the disease.

Materials and methods

In order to analyse the latest data on approaches to complex diagnostics, symptomatic manifestations, features of pathogenesis and differential diagnosis of neuro-endocrine manifestations of combined acute TBI, a systematic analysis of research papers in the field of emergency medicine, neurology, internal medicine, endocrinology, psychiatry, and pathophysiology was carried out. For the selection of data for the purpose of subsequent analysis, a number of scientific evidence-based publications were selected, which were published by relevant and reliable periodical medical publications with a high impact factor. The selection of processed papers and clinical recommendations was based on the principle of using advanced, relevant, and evidence-based research data. The analysis includes long-term observations of voluminous cohorts of patients with TBI of varying severity, randomised clinical trials (with groups of patients who underwent experimental treatment regimens using hormone therapy), statistical work (with an assessment of the clinical status of patients with TBI with a predominance of a specific endocrine syndrome; with a study of the prevalence of neuroendocrine symptoms of TBI in specific ethnic groups) and clinical cases (with complicated or non-standard clinical manifestations and the course of TBI on the part of the endocrine, nervous or cognitive system). Meta-analyses were also included in the work, which covered large cohorts of patients in the projection from 8 months to 5 years of observation of the development of the acute and remote phase of TBI under the supervision of supervising doctors. The study includes meta-analyses

with an emphasis on the diagnosis and symptoms of neuro-endocrine disorders during the course of TBI. Part of the analysed scientific papers is devoted to the applied new experimental models for the study of the molecular mechanisms of the course of TBI, which were carried out on experimental animals and are potentially effective methods for introduction into clinical practice [15].

Thus, the study includes scientific papers published in 2019-2023 in specialised and evidence-based medical publications in Uzbekistan, Europe, and the United States, which displayed new data on the pathogenesis, diagnosis and symptomatic manifestations of neuro-endocrine disorders in acute concomitant TBI. Academic search engines and resources such as Google Scholar, ResearchGate, PubMed, Medscape, Science Direct and EBSCO were used to search for articles. In most cases, material from open databases of scientific data from licensed publishing or search platforms for scientists is used. During the work, the identification of the researcher, that is, the author of the study, was carried out – an authorised login, search and work (quoting, studying, gaining access to full-text material) was used on platforms. Identified work with databases of scientific publications allows excluding duplication of the results of the same scientists in different publications, related articles (which duplicate the results obtained) that are irrelevant by the date of publication or the purpose of the study, as well as to quickly check the citation and impact factor indicators of both the work itself and the medical publication. In addition to filtering the robot by publication date, a number of keywords were also used during the search. This helped exclude articles and guidelines that dealt with infectious and hereditary pathologies of the brain, which were not the purpose of this study.

Results

According to A. G. Kolias et al., brain injuries include a variety of criteria for the structure, intensity, volume, and magnitude of the impact (or bruises) on the brain of a patient with a traumatic effect on cells, tissues and structures of the brain [16]. To date, endocrine disorders are no longer considered rare or uncharacteristic complications of acute TBI, as follows from the hypothesis and the results obtained by C. Mahajan et al. in 2023 [12]. The statistical prevalence of endocrine disorders in combined TBI varies in different scientific papers depending on the time frame of traumatisation, the type of diagnostic methods used, and the variability of hormonal disorders and is detected on average in every fifth patient hospitalised with TBI [13]. Neuroendocrine conditions on the background of acute TBI include both direct mechanical, traumatic effects on the anatomical integrity of the central organs of endocrine regulation, and secondary factors mediated by increased cranial pressure, the development of swelling of brain tissues, neuro-inflammatory and neuro-degenerative processes in the central nervous system. Violation of hemostasis of endocrine regulation affects not only the central axis of hormonal regulation, but also affects the tissues of the internal environment of the body, which manifests itself both in the acute and remote phase of the course of TBI.

Hypopituitarism

The statistical distribution of cases of diagnosis of hypopituitarism on the background of acute TBI changes with the time of patient management and is estimated at about a quarter of all diagnosed TBI per year, as M. Kalas et al. indicate in their paper in 2023 [17]. Scientific data from M. Bensalah et al. in 2020 show that more than a third of patients have irreversible lesions of the adenohypophysis after a TBI, the severity of which increases with repeated injuries of the central nervous system [18]. Their diagnosis requires a comprehensive approach that includes both imaging methods (computed tomography (CT), magnetic resonance imaging (MRI)) and biochemical methods that determine the hormonal status of the patient. According to the analysed papers, hypoproduction of adenohypophysis hormones is more common in the clinic of combined TBI than isolated deficiency of hormone secretion of the posterior pituitary [11,16]. According to M. Bensalah et al., the overall risk of hormone-producing disorders of the central hypothalamic-adenohypophysial axis after TBI in female patients is higher compared to male patients, which is proven by systematic determinations of changes in hormone levels at different stages of TBI [18]. The untimely diagnosis of hypopituitarism in the acute phase of TBI is often associated with the manifestation of nonspecific symptoms from the musculoskeletal, nervous, and cardiovascular systems. Hypodiagnosis of hypopituitarism in the remote phase of the patient's management or even the non-manifestation of central endocrinological disorders can serve as a threat to the quality of life and the rehabilitation process in patients. According to W. You et al. in their study, the severity of the traumatic factor, age, the presence and volume of

subarachnoid haemorrhages (which are diagnosed using MRI), disorders of neuro-somatic conduction (diagnosed using functional tests and encephalogram), the presence of fractures of the skull base are associated with an increased risk of adenohypophysis dysfunction [19]. According to J. Martin-Grace et al., hypopituitarism due to TBI is often accompanied by insufficiency of the hormone-synthesising function of the adrenal cortex, which is manifested by an imbalance of ions in the blood serum and a malfunction of the glomerular apparatus of the kidneys [20]. It is important to diagnose these conditions at the hospital stage of management of patients with TBI, since in the long-term period these manifestations can be diagnosed as isolated conditions not associated with a previous TBI.

The central endocrine axis "hypothalamus-adenohypophysis-adrenal glands" as the controlling basis of systemic homeostasis of the internal environment of the body can be significantly damaged by combined brain injuries both directly and indirectly [20]. According to N. Sabet et al., on the one hand, a direct mechanical effect on the anatomical structures of the central endocrine axis is possible: parts of the hypothalamus, adenohypophysis, or due to a fracture of the bones of the base of the skull with subsequent haemorrhages, which are visualised on CT and MRI [21]. From another point, the most topographically vulnerable area for traumatic and compression injuries in TBI in the central endocrine axis is the diaphragm of the sella turcica, since there are long somatic vessels that supply blood to the distal and anterior parts of the pituitary gland and drain the capillary system of the pituitary pedicle [20]. Clinically, this may manifest itself in the form of ischemic necrosis of the pituitary lobe, accompanied by hypopituitarism [19]. Since the vessels passing through the sella turcica nourish the antero-lateral lobe of the pituitary gland, whose cells produce somatotropin, follicle-stimulating hormone and luteinising hormone, the primary signs of hypopituitarism will appear by hypoproduction of these hormones [21]. Primary hypopituitarism, which according to A. Loggini et al. are most often manifested by hypoproduction of somatotropic hormone, which will be clinically accompanied by hypoproduction of adrenocorticotropic hormone, gonadotropic hormones, and thyroid stimulating hormone, respectively affecting the homeostasis of the adrenal glands, sex glands, and thyroid thyrocytes [22].

The anatomical region below the diaphragm of the sella turcica, through which the shortened portal arteries and veins of the central endocrine axis pass, nourish the medial and anterior regions of the adenohypophysis and clinically have lower risks of rupture due to mechanical impact and necrosis, according to statistical data [15,20,24]. Thus, in the clinical picture, hypopituitarism will be less often accompanied by a deficiency of thyroid-stimulating and adrenocorticotropic hormone, which feed on these shortened portal arteries and veins.

In the development of hypopituitarism against the background of acute TBI, anamnestic data of past cases of TBI in the patient also play an important role, especially against the background of increased pressure due to repeated trauma. Research on athletes by A. Muravskiy et al. show that professional boxers who undergo regular head injuries have elevated titers of circulating antihypophyseal and antihypothalamic antibodies [25]. As a result of combined acute TBI in patients with chronic CNS injuries, the development of neuro-endocrine disorders may become the leading manifestations (after neurological) due to autoimmune reactions against the background of elevated antibodies to central endocrinological organs [26]. This cohort of patients should be more thoroughly diagnosed for background conditions of autoimmune reactions to CNS tissues.

The degree of manifestation of hypopituitarism against the background of acute TBI also depends on the genetic predisposition. Genotypically determined background inflammatory, autoimmune, and neurodegenerative processes increase the permeability of the blood-brain barrier both from ependymocytes and macroglia, and from the endothelial lining of blood vessels and the basement membrane, as indicated by D. Pavlovic et al. [27]. The altered permeability of the barrier allows the antigens of the central organs of endocrine regulation (hypothalamus, pituitary gland, epiphysis) to circulate in the blood, which triggers the mechanisms of production of the corresponding antibodies to these organs [25,27]. Acute TBI leads to a sharp increase in the titer of antibodies, which as a result is accompanied by hypopituitarism, which was investigated by E. Javidi and T. Magnus [28]. Other studies have identified a specific ApoE gene, polymorphisms and mutations in which can serve as clinical predictors of the type of course and severity of the consequences of TBI in a patient [29]. Data by P. Muza et al. suggest that the polymorphism of the ApoE 3/E3 type indicates the predominance of neurological complications of TBI compared to endocrinological ones, that is,

with a minimal probability of hypopituitarism [30]. Study by P. Muza also points out that ApoE polymorphism is also characteristic of neurodegenerative pathologies of the central nervous system, but in the focus of TBI, especially recurrent ones, it significantly correlates with an increased risk of developing chronic traumatic encephalopathy. The authors of a number of genetic studies claim that the determination of matrix RNA in blood plasma at the time of admission of a patient with acute TBI allows differentiating a cohort of patients with increased risks of hypopituitarism and neuro-endocrine complications [31,32].

The problem of clinical diagnosis of hypopituitarism consists in the variability of clinical manifestations in both acute and chronic phases, as well as the presence of nonspecific subjective manifestations. In the acute phase of TBI, impaired consciousness, refractory hypotension, decreased muscle reflexes and deficiency of adenohypophysis hormones may not be diagnosed from the point of view of endocrinological syndrome, whereas hypoproduction of gonadotropins may appear in the chronic phase [13]. Hypopituitarism is often diagnosed in the chronic phase, which according to N. Glynn and A. Agha are currently a serious problem in the management of patients with TBI, since hormonal imbalance affects a number of peripheral organs of the endocrine system, which significantly worsens the quality of life and rehabilitation outcomes [33]. In this phase, symptoms of deficiency of somatotropin, gonadotropins, thyroid-stimulating (violation of basal metabolism, dyslipidemia) and adrenocorticotropic hormone prevail [33,34]. In addition to changes in the panel of adenohypophysial hormones, it is important to note the insulin resistance developing against the background of TBI, which is manifested by an increased fasting glucose level [31]. As a result, hypogonadism and hypothyroidism due to hypopituitarism can disrupt cognitive functions, including memory, socialisation and the development of depressive disorders.

Diabetes insipidus

Another type of manifestation of neuroendocrinological disorders in acute TBI is represented by DI. This pathology develops against the background of central (neurological) or peripheral (nephrotic) acute conditions as a result of impaired functioning of the arginine-vasopressin system [35]. In patients with acute TBI, there are two pathophysiological ways of developing DI: with central damage to the hypothalamus or with nephrotic insufficiency developing against the background of the oedematous syndrome, respectively. Dysregulation of vasopressin leads to violations of the water-electrolyte and osmotic balance in the circulating body fluids (blood, lymph, cerebrospinal fluid).

Topographically, this hormone is synthesised in the central parts of the endocrine system – the neurosecretory cells of the nuclei of the anterior group of the hypothalamus, and is secreted through the posterior part of the pituitary gland [36]. A. Garrahy and C. J. Thompson show that the development of primary central DI is not always associated with direct traumatisation of hypothalamic-pituitary structures, whereas the symptoms of polyuria and polydipsia syndrome indicate a violation of secretion or sensitivity to vasopressin [37]. These manifestations may also have a transient character, manifested in the acute phase of TBI. Primary central DI can also be caused by acute TBI of different localisation, meningitis, and encephalitis [36,38]. Therefore, it is important to distinguish between DI against the background of predisposing conditions of infectious or inflammatory genesis and acute central DI conditioned by combined TBI.

Study by A. Gempeler et al. show that DI in the observed cohort of patients (study duration – 6 years) with combined TBI develops on the second day after injury [38]. Thus, the authors attribute this condition to early complications of TBI, which in almost 30% of cases observed by scientists led to a fatal outcome. The authors attribute increased intracranial pressure, cerebral oedema, penetrating wounds of the skull and subarachnoid haemorrhages to predisposing factors to the development of DI in patients with combined acute TBI.

Morphologically, with a combined brain injury, the pathogenesis of DI is triggered due to frontal-occipital dislocation of brain tissues, violation of the integrity of the portal blood supply system of the hypothalamus axis or traumatisation of the infindibular part of the hypothalamic-pituitary system. According to R. M. Tudor and C. J. Thompson, DI on the background of TBI develops in every fourth patient with a manifestation in the form of dysnatremia, therefore, in the acute phase it is important to differentiate DI with primary adrenal insufficiency [39]. Significant intracranial lesions in the form of haemorrhages and haematomas are accompanied by a sharp increase in intracranial

pressure, which can lead to transient disorders of the hypothalamic-pituitary axis. As indicated in their 2022 paper by M. Tomkins et al., the development of DI in TBI significantly improves clinical outcomes and rehabilitation processes due to an increased risk of early complications in the form of refractory hypernatremia, general tissue oedema, seizures, decreased ventricular contractility, and encephalopathy [40]. With the progression of DI, stable water loss leads to hypovolemic hypernatremia, which therapeutically requires maintaining a stable volume of circulating blood, often with the use of vasoconstrictor drugs.

Hypothalamic syndrome

Hypoxic, apoptotic, and dysmetabolic processes play an important role in the development of TBI along with traumatic damage to neurons and neuroglia [2]. Combined acute TBI causes an imbalance of oxidative, metabolic and circulatory reactions, which exacerbates the existing background pathologies and often leads to terminal hypoxia of the brain, which manifests itself in violation of general clinical, biochemical, and functional disorders of the organs [27]. Some researchers distinguish the term “hypothalamic syndrome" (HS) or “hypothalamic dysfunction” as a collective definition of neuroendocrine disorders caused by both internal hypoxic or traumatic and external factors affecting the neurosecretory neurocytes of the hypothalamus and the portal system of its blood supply. According to Z. S. Gan et al., the most common etiological cause of HS is TBI, ahead of infectious diseases of the central nervous system [41]. In patients with combined acute TBI, the hydrodynamic effect of cerebrospinal fluid on the structures of the central nervous system increases, including hormone-producing cells of the anterior and medical groups of the hypothalamus nucleus, which are anatomically projected to the bottom of the third ventricle, as indicated by Z. Gan et al. [41]. Neurosecretory cells of the hypothalamus secrete vasopressin and oxytocin, damage to which worsens neuroprotective and anti-inflammatory reactions of nervous tissue in TBI [39,42]. Experimental modelling of TBI in rats, conducted by W. Chen et al. showed that when exogenous oxytocin is administered to damage the nuclei of the hypothalamus, there is a decrease in neuro-behavioural and convulsive symptoms, as well as a decrease in the permeability of the haemato-encephalic barrier [43]. Compensation of oxytocin deficiency in TBI in the experiment showed statistically significant correlations with lower risks of neurodegenerative conditions, compared with the group of animals that did not receive oxytocin. Data published by M. A. Panaro et al., according to which oxytocin participates in the regulation of central inflammatory responses and neuroinflammation after hypoxic states of the brain, pro-inflammatory reactions of microglia of CNS tissues, and the activity of synaptic transmission between multipolar neurocytes, which determines its importance as a clinical marker of the course of HS in patients with TBI [44].

Secondary brain damage in acute TBI occurs against the background of significant oedema of the central nervous system tissues, which leads to unfavourable outcomes in the long-term period of the disease. Aquaporins, highly selective transmembrane channels of neurocyte cells, take part in the pathogenesis of the development of post-traumatic oedema of brain tissues. The study by K. Rauen et al., shows the important role of brain cell aquaporins in the development of oedema in TBI by activating specific V1-a receptors in an experiment [45]. Data obtained by K. Rauen is confirmed by E. Zeynalov et al.: activation of the V1-a membrane receptor is responsible for vasoconstriction; V1-b receptor for the regulation of cognitive and behavioural reactions; V2 receptor for the activity of endocytic processes in the nephrogenic epithelium of the kidneys [46]. According to E. Zeynalov et al., in most patients with acute TBI, cerebral oedema develops against the background of vasopressin hyperproduction (with activation of V1-b receptors) and hyponatremia as a result of the syndrome of inadequate secretion of pituitary antidiuretic hormone, which emphasises the need for systematic monitoring of the ionogram and hormonal panel during TBI treatment. A retrospective analysis lasting three years, which included more than 500 patients with acute TBI who received therapy with vasopressin, showed a statistically significant decrease in the number of deaths in patients of the experimental group. N. Dhillon et al. recommend the use of therapy including vasopressin drugs in patients with an increased risk of secondary complications during the treatment of TBI under the control of clinical indicators, that is, in a hospital setting [47].

The differential diagnosis of the above-mentioned neuroendocrinological syndromes such as deficiency of hormone-secreting function of the hypothalamus and pituitary gland is shown in Table 1. As follows from the data of scientific papers, the determination of hormone and ion levels has a

decisive role in the diagnosis of neuro-endocrine disorders, since subjective symptoms are variable and nonspecific [20,32,35,43].

Table 1. Differential diagnosis of neuroendocrine disorders in patients with combined acute traumatic brain injuries

No	Clinical signs	Hypothalamic syndrome	Diabetes insipidus	Hypopituitarism
1	Headache	Present in the anamnesis	Missing in anamnesis	Absent
2	Arterial vascular pressure	Within the age norm / increased in the vegetative-vascular variant of the course	Elevated at the time of the disease	Reduced at the time of the disease
3	Glucose tolerance test	Impaired glucose tolerance	Impaired glucose tolerance	Impaired glucose tolerance
4	Blood C-peptide	Elevated	Within the age limit	Elevated
5	Serum cortisol	Elevated	Within the age limit	Reduced
6	Plasma aldosterone	Elevated	Within the age limit	Reduced

Cognitive and behavioural disorders

In patients with combined acute TBI, neuroendocrine disorders are associated not only with physiological changes in hormone-synthesising cells, but also with cognitive, emotional and behavioural disorders due to traumatisation and deficiency of somatotropin, thyroid-stimulating and adrenocorticotropic hormones [48]. A. Sander et al. long-term follow-up has shown that psychoemotional changes in patients with TBI affect both the rehabilitation process of the victim and social reintegration with the restoration of working capacity in the long-term management of the patient [49]. Among the most common consequences of the psycho-emotional sphere due to the influence of traumatic factors on the brain tissue and central (regulating) endocrine organs, N. Turner et al. distinguish long-term social maladaptation, depressive disorders, and, more rarely, intellectual and psychological dysfunction [50]. In the chronic period of TBI, cognitive impairments may develop as a result of post-traumatic stress disorder against the background of a central hormonal imbalance [26]. Thus, the management of a patient with TBI needs an integrated approach involving psychiatric specialists for the differential diagnosis of psychological and psychiatric conditions and the choice of the most appropriate treatment tactics in each case.

Despite the fact that psychiatric and cognitive symptoms in patients with TBI are often considered in the complex of post-concussion syndrome, studies have been published that indicate an increased risk of neuropsychiatric disorders in patients with acute TBI and hypofunction of the central endocrine glands, compared with patients with the normal hormone-secreting function of the hypothalamus and pituitary gland [26,27,51]. Neuropsychiatric disorders in such patients are manifested by a deficit of attention and memory with mild degrees of traumatisation; impaired speech and visual-spatial constructive skills with severe acute injuries. Study of patients with acute TBI by K. Silveira and C.M. Smart showed that among the survivors of TBI in the distant phase of the disease, symptoms of depression were diagnosed in more than 45% of correspondents, and 40% reported suicidal thoughts [48]. A similar study by L. de. Munter et al. confirm that psychological distress syndrome is common in patients with TBI during the first year of the disease [52]. Prognostic factors of the development of psycho-cognitive disorders in patients with TBI include the state of the patient's psychoemotional sphere before traumatisation, psychological complaints at the time and after injury, reduced psychological flexibility and adaptability, and moral instability. Timely diagnosis of psychological problems after TBI can improve the patient's quality of life, socialisation activity, and improve cognitive processes.

Conclusions

The most common clinical manifestation of neuroendocrine pathologies in combined acute traumatic brain injuries are hormone-deficient and neuropsychiatric symptoms. The clinical consequences of acute brain injuries are heterogeneous and include both physical and cognitive disorders of a transient or chronic type, depending on the presence of a history of brain injuries, the duration and intensity of the traumatic factor. Among the pathogenetic factors affecting the involvement of hormonal disorders in the clinic of traumatic brain injuries, secondary hypopituitarism, hypothalamic syndrome and diabetes insipidus are distinguished. A post-traumatic decrease in the synthetic activity of hormone-producing pituitary cells in the form of somatotropin deficiency is often observed both in the acute and post-traumatic phase of patient management. Inhibition of synthetic activity of chromatolphilic cells of the adenohypophysis in brain injuries develops due to ischemic damage to structures in the area of the sella turcica, reactions of immunocompetent cells, haemorrhages and disorders of the portal blood supply system of the hypothalamic-pituitary axis. The most frequent disorders of the hypothalamic-pituitary axis in patients with acute brain injury in the acute and chronic stages are manifested by a deficiency of somatotropin, gonadotropin, and adrenocorticotropic hormone; a deficiency of thyroid-stimulating hormone, which affects the imbalance of the main metabolic metabolism and dyslipidemia. Damage to neuroendocrine regulation can lead to death, dysnatremia, terminal systemic hypotension, and disability. In the chronic period of the course of brain injuries, psychological disorders in the form of depressive syndromes, suicidal thoughts and social disintegration can develop as a result of post-traumatic stress disorder against the background of central hormonal imbalance. Further studies of this problem in order to study the mechanisms of occurrence of endocrinological damage in brain injuries and structures of the central nervous system provide experimental modelling of brain damage of various etiologies. The obtained data allow improving the early detection and diagnosis of secondary neuroendocrine disorders against the background of traumatic brain injuries, and increasing the effectiveness of complex treatment and the quality of life of patients in the future.

Authors' contribution

Conceptualization, K.K. and F.Kh.; methodology, K.K.; software, Y.K.; validation, K.K., F.Kh., and Z.Kh.; formal analysis, K.K.; investigation, F.Kh.; resources, G.I.; data curation, Y.K.; writing—original draft preparation, K.K.; writing—review and editing, F.Kh. and Z.Kh.; visualization, Y.K.; supervision, K.K.; project administration, G.I.; funding acquisition, K.K. All authors have read and agreed to the published version of the manuscript.

Funding source

This research received no external funding.

Ethics approval

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of Tashkent State Medical University. Ethics approval was obtained for all study procedures.

Consent for publication.

Informed consent was obtained from all subjects involved in the study for publication of their data.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Acknowledgments

The authors would like to express their sincere gratitude to Andijan State Medical Institute for providing scientific and academic support during the preparation of this review article. The authors also acknowledge all researchers and clinicians whose published studies contributed to the analysis of neuroendocrinological disorders associated with traumatic brain injuries.

Conflict of interest

The authors declare no conflict of interest.

Abbreviations

TBI	Traumatic Brain Injury
CNS	Central Nervous System
DI	Diabetes Insipidus
HS	Hypothalamic Syndrome
CT	Computed Tomography
MRI	Magnetic Resonance Imaging
ACTH	Adrenocorticotropic Hormone
TSH	Thyroid-Stimulating Hormone
GH	Growth Hormone
FSH	Follicle-Stimulating Hormone
LH	Luteinizing Hormone
CSF	Cerebrospinal Fluid
ApoE	Apolipoprotein E
RNA	Ribonucleic Acid
GABA	Gamma-Aminobutyric Acid

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