Original paper

Endocrine disorders in children with craniopharyngiomas during the preoperative period

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Abstract

Introduction: The aim of the study was an assessment of the type and incidence of endocrine disorders against the background of general, neurological and ophthalmological symptoms, observed during the preoperative period in children with craniopharyngioma (CPH).

Material and methods: The study group comprised 20 children with CPH operated on at the Department of Neurosurgery, Polish Mother's Memorial Hospital-Research Institute in Lodz during the years 1990-2003. Medical records of the involved patients and laboratory tests results were the subject of a thorough analysis.

Results: Endocrine disorders occurred in 13 out of 20 patients, most often: short stature (9/20), obesity (6/20), delay of puberty (5/20) and diabetes insipidus (2/20). The functional status of the thyroid gland and of the adrenal cortex was evaluated in 7 patients only, finding secondary hypothyroidism in 5 and secondary adrenocortical insufficiency in 4. General symptoms included: headaches (13/20), vomiting (5/20), behavioural changes (4/20). Ophthalmological symptoms included: restricted visual field (6/20), changes at the fundus of the eye (8/20) and deteriorated visual acuity (8/20). Neurological symptoms included: cranial nerves paresies (10/20), gait and balance disturbances (2/20), hemiparesis (3/20).

Conclusions:

1. In the preoperative period, a considerable number of children with CPH, reveal functional disorders of the pituitary, manifested by growth retardation, secondary hypothyroidism and adrenocortical insufficiency.
2. The hormonal evaluation, especially of the thyroid gland and adrenal cortex, should routinely be performed in children with CPH before the surgery, due to the necessity of an appropriate hormonal replacement therapy in cases of secondary hypothyroidism and/or hypoadrenia.

Key words: craniopharyngioma, children, endocrinological disorders, preoperative period, growth hormone deficiency.

Introduction

Craniopharyngioma (CPH) is the most frequently observed tumour within the hypothalamic-pituitary region, constituting between 6-9% of all brain

tumours in the population of developmental age [1]. It is a benign (non-malignant) tumour, revealing a fairly high postoperative survival rate [2]. However, in case of advanced tumour growth, the degree of resulting lesions in the pituitary, the hypothalamus, the visual or nervous pathways, may be significant. Then, despite the good outcome of the applied neurosurgical treatment, disturbed functions of the above mentioned structures persist for the rest of the life of the affected patient. Therefore, possibly the earliest diagnosis of the disease, followed by prompt application of the surgical treatment, are significant factors to improve the prognosis (the number of complications and the quality of patient's life) [2].

Clinical symptoms, occurring prior to CPH diagnosis, depend on tumour size and localisation [3]. Increasing tumour mass, nervous tissue oedema and disturbed flow of the cerebrospinal fluid result in the increased intracranial pressure, inducing – in turn – symptoms such as headaches, vomiting, meningeal signs and papilloedema but also squint and double vision, the latter two resulting from the high sensitivity of the abducent nerves to intracranial pressure.

Damage of the tumour-affected part of the brain and oedema and/or relocation of the structures neighbouring with the tumour, are responsible for local neurological symptoms. Lesions of the optic nerve impairs visual acuity, leading – in severe cases – to total blindness. Moreover, damage of the optic system introduces the constriction of the visual field.

In cases of either lesions of the pituitary or pressure exerted onto the gland, its stalk or onto the hypothalamus, endocrinological symptoms occur, associated with abnormal secretion of the hypothalamic-pituitary hormones. Isolated growth hormone deficiency (GHD) or multiple pituitary hormone deficiency (MPHD), diabetes insipidus (DI) and/or hyperprolactinaemia may reveal. Obesity is also a frequent disorder, associated with an abnormal control of the hunger and appetite brain regulative centres, located in the ventral medial nucleus of the hypothalamus [4, 5].

The aim of the study was an evaluation of the type and incidence of endocrinological disorders, vs. general, neurological and ophthalmological symptoms, observed during the preoperative period in children with CPH.

Material and methods

A retrospective analysis comprised data from medical records of 20 children (11 boys and 9 girls), their age ranged from 3.3 to 17.4 years (the mean age±SD: 11.2±4.97 years). All the patients were operated for CPH during the years 1990-2003 at the Department of Neurosurgery, Polish Mother's Memorial Hospital – Research Institute, Lodz, Poland.

Patient's history, current complaints, actual body weight and height, the sexual maturation stage, following Tanner's scale [6], the physical examination, including the results of neurological and ophthalmological consultations and results of laboratory tests were taken into consideration.

In each case, MRI or CT scanning of the brain was performed. The diagnosis of CPH was confirmed in postoperative histopathological evaluation.

On the basis of available data, the height standard deviation score (HSDS) and body mass index (BMI) standard deviation score (BMI SDS) were calculated. HSDS and BMI SDS are the relative indexes, expressing – respectively – the height or BMI of the examined child by the number of standard deviations from the mean values for age and sex of the child [7].

Short stature was diagnosed, when HSDS was below (-2.0). Obesity was determined, if BMI SDS was above (+2.0). Delayed puberty was diagnosed, when no clinical symptoms of sexual maturation were observed in girls after 13 years of life and in boys – 1 year older. Diabetes insipidus was diagnosed on the basis of typical clinical symptoms (polyuria and polydipsia), as well as of the increased serum osmolarity and hypostenuria. Urine concentration test was not performed in any of those cases.

Growth hormone deficiency was diagnosed, when the maximal growth hormone (GH) concentration was below 10 ng/mL in two stimulation tests (after clonidine and glucagon). Secondary hypothyroidism was diagnosed by decreased serum thyrotropin (TSH) and free tyroxine (FT_4) concentrations, while the diagnosis of secondary adrenocortical insufficiency was based on the decreased serum cortisol concentration at 8.00 a.m.

Multiple pituitary hormone deficiency was diagnosed, when GHD and secondary hypothyroidism and/or secondary adrenocortical insufficiency were diagnosed simultaneously.

The observed symptoms and disorders were grouped as follows:

1. General symptoms – complaints reported by the child or its parents.
2. Neurological disorders – found in history or present during the neurological examination.
3. Ophthalmological disorders – found in the ophthalmological examination.
4. Endocrinological disorders – found in the physical examination, also results of laboratory investigations.

Results

A detailed list of symptoms and data of brain CT or MRI scanning for particular patients, performed before CPH surgery, were presented in Table I.

1. General symptoms

Headaches were found in 13 children, with accompanying vomiting in 5 cases. No relationship was observed between the headaches or vomiting and the child's age, tumour localisation or size. In

Table I. A detailed list of symptoms from particular arbitrary groups and the data of brain CT or MRI scanning, performed before CPH removal

Nb	Sex	Age (years)	General symptoms	Neurological disorders	Ophthalmological disorders	Endocrinological disorders	Localisation of tumour (CT or MRI scanning)
1	F	3.3	headache, vomiting, behavioural changes	gait and balance disturbances, motor aphasia, unilaterally positive Babinski's sign	papilledema and optic nerve atrophy	hypostenuria	suprasellar region, indentation into ventricle III
2	F	4.8	–	anisocoria	deteriorated visual acuity (unilateral blindness)	diabetes insipidus, obesity	suprasellar region, expansion into interpeduncular fossa and into III ventricle
3	M	4.8	headache	anisocoria, squint	papilledema and optic nerve atrophy	–	sella turcica and suprasellar region
4	F	7.9	headache	anisocoria, restricted upward mobility of the right eye	papilledema and optic nerve atrophy, deteriorated visual acuity (unilateral blindness)	–	sella turcica and suprasellar region
5	F	8.1	–	facial nerve paralysis, unilateral hemiparesis	–	–	occupied frontal, parietal and temporal lobe, impact on lateral ventricles, pons and ventricle III
6	F	9.1	–	–	deteriorated visual acuity, constriction of visual field	obesity	sella turcica and suprasellar region, penetration into hypothalamus, compression the optic chiasm
7	M	10.2	hypersomnia	–	deteriorated visual acuity (bilateral blindness)	–	suprasellar region expansion into III ventricle
8	M	11.3	headache, vomiting	double vision	constriction of visual field	short stature, adrenocortical insufficiency, hypothyroidism, obesity	suprasellar region, expansion into III ventricle, compression of the optic chiasm
9	F	11.7	–	facial nerve paralysis (2x)	–	short stature, hypothyroidism, adrenocortical insufficiency	sella turcica and suprasellar region
10	F	11.9	–	squint, unilateral hemiparesis	papilledema and optic nerve atrophy, constriction of visual field	short stature	sella turcica and suprasellar region expansion into III ventricle
11	F	12.4	headache, hypersomnia	hypoaesthesia, hearing loss, gait and balance disturbances	–	obesity	suprasellar region, compression of optic chiasm, displaced left cerebellum peduncle, stem and ventricle IV
12	M	12.8	headache, vomiting	–	papilledema and optic nerve atrophy, constriction of visual field	short stature, adrenocortical insufficiency, hypothyroidism, hypostenuria	sella turcica and suprasellar region, expansion into III ventricle

Table I. (continuation)

Nb	Sex	Age (years)	General symptoms	Neurological disorders	Ophthalmological disorders	Endocrinological disorders	Localisation of tumour (CT or MRI scanning)
13	M	13.9	headache, vomiting	–	papilledema and optic nerve atrophy, constriction of visual field	short stature, delay of puberty	suprasellar region expansion into III ventricle
14	M	14.6	headache	–	–	short stature, delay of puberty, obesity, hypostenuria	suprasellar region, indentation into III ventricle
15	M	14.9	–	nystagmus	deteriorated visual acuity	short stature, delay of puberty, hypothyroidism, adrenocortical insufficiency, obesity	sella turcica and suprasellar region, compression of optic chiasm
16	M	16.2	headache	meningeal signs	deteriorated visual acuity	short stature, hypothyroidism, delay of puberty, diabetes insipidus	suprasellar region, compression of optic chiasm
17	F	16.5	headache, vomiting	anisocoria, nystagmus, unilateral hemiparesis	papilledema and optic nerve atrophy, deteriorated visual acuity (bilateral blindness)	short stature, delay of puberty	suprasellar region, compression of optic chiasm
18	M	17.1	headache	–	papilledema and optic nerve atrophy, deteriorated visual acuity, constriction of visual field	–	sella turcica and suprasellar region
19	M	17.2	headache	seizures	–	–	suprasellar region
20	M	17.4	headache, hypersomnia	meningeal signs, seizures, decreased muscular tone	–	–	sella turcica and suprasellar region

4 patients, behavioural changes were noted (most often hypersomnia); hypersomnia coexisted with headaches and vomiting in 3 cases, while only in 1 case, it was an isolated symptom. In each case, the presence of those symptoms had been observed by parents 0.5-1.5 years before the diagnosis (Figure 1).

2. Neurological disorders

Neurological symptoms occurred in 14 out of 20 children (Figure 2). Seizures in history occurred in 2 children. Positive meningeal signs were observed in 2 children. Lesions of the cranial nerves were found in 10 patients. Most frequently disturbed functions of the oculomotor nerves (7 patients) were observed: squint in 2 patients, restricted upward mobility of the right eye – in 1, double vision – in 1 and anisocoria – in 4 patients. In 1 girl, paresis of the 2nd and the 3rd branch of the facial nerve (VII) was found, while in another patient, similar incidents of the facial nerve (VII) paralysis occurred in the past. In 1 patient, discrete, unilateral facial hypoaesthesia was noted with unilateral hearing loss. In that girl, the tumour, together with affecting the suprasellar region, also displaced the left cerebellum peduncle, the brain stem and ventricle IV. Nystagmus was observed in 2 patients.

In examination of the locomotor system, a decreased muscular tone was observed in 1 patient and unilateral hemiparesis – in 3. Gait and balance disturbances occurred in 2 girls. Moreover, in one of them, motor aphasia and unilaterally positive Babinski's sign were noted. In the other girl, there were also the – mentioned before – hearing loss and facial hypaesthesia. The case of the girl with hemiparesis and with paresis of the 2nd and the 3rd branch of nerve VII was associated with the localisation of the big size tumour in 3 lobes: frontal, parietal and temporal.

In most of these cases, the presence of disorders mentioned above, was the direct reason of symptoms reported to the doctor and – eventually – the following brain tumour diagnosis.

3. Ophthalmological disorders

Ophthalmological disturbances were found in 13 out of 20 children (Figure 3). In 8 patients, visual

acuity was deteriorated (including uni- or bilateral blindness in 4 of them). In 6 patients, constriction of the visual field was found; while only in one case, it was bitemporal hemianopsia. Changes at the fundus of the eye, manifested by optic papilla pallor were found in 8 patients, while in two of them no changes were noted, regarding either the vision field or visual acuity. The occurrence of the prevalent part of the aforesaid symptoms was also the reason of the first visit to the ophthalmologist followed by diagnostics directed into CPH.

4. Endocrinological disorders

Endocrinological disorders occurred in 13 out of 20 patients (Figure 4). Short stature was diagnosed in 9 children. In 3 of them, evaluation of GH secretion was performed and – after that – GHD was diagnosed in all 3 cases. In 5 patients (out of possible 8), delayed puberty was found; in each case with accompanying short stature. No data regarding the course of sexual maturation were available for 1 patient. In the other 2 patients with normal sexual maturation, CPH was revealed relatively late (both patients were above 17 at the time of the diagnosis). The other children were in prepubertal stage, however, they were at the age, in which the lack of sexual maturation symptoms is a physiological feature and in any case it is not a pathological observation. Obesity was noted in 6 children. In 2 cases, it was an isolated symptom, in other 2 cases, it accompanied MPHD. Thyroid and adrenal functions were evaluated in the preoperative period in 7 patients. In 5 of them, secondary hypothyroidism was found, while in other 4 – secondary adrenocortical insufficiency was observed. In each child with diagnosed adrenocortical insufficiency and/or hypothyroidism, GHD or short stature was a parallel symptom. Thus, in 5 cases MPHD was diagnosed.

Diabetes insipidus was found in 2 children, while in other 3 – hypostenuria was observed, with no clinical symptoms of DI. In 3 of these cases, DI or hypostenuria were observed in children with MPHD.

Summarizing, in each of 9 children with short stature, growth retardation had been observed by

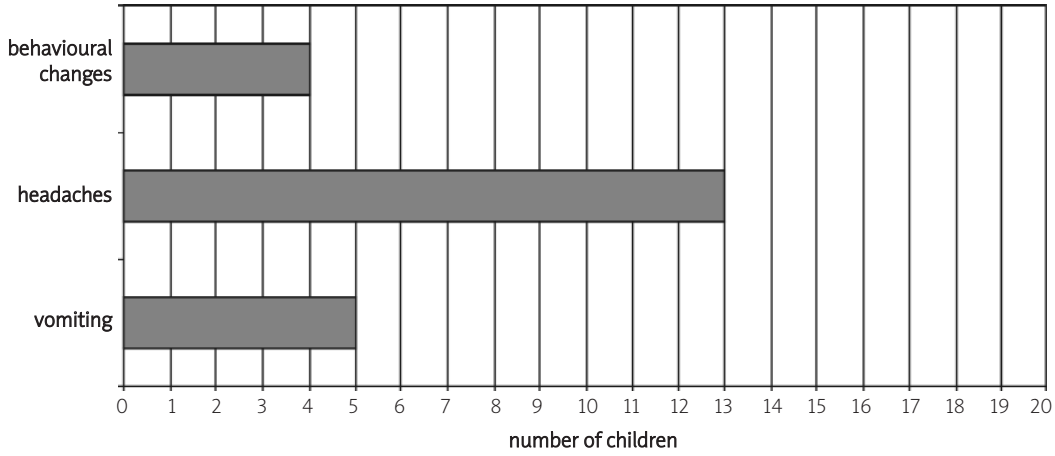

Figure 1. The incidence of particular general symptoms in the studied population

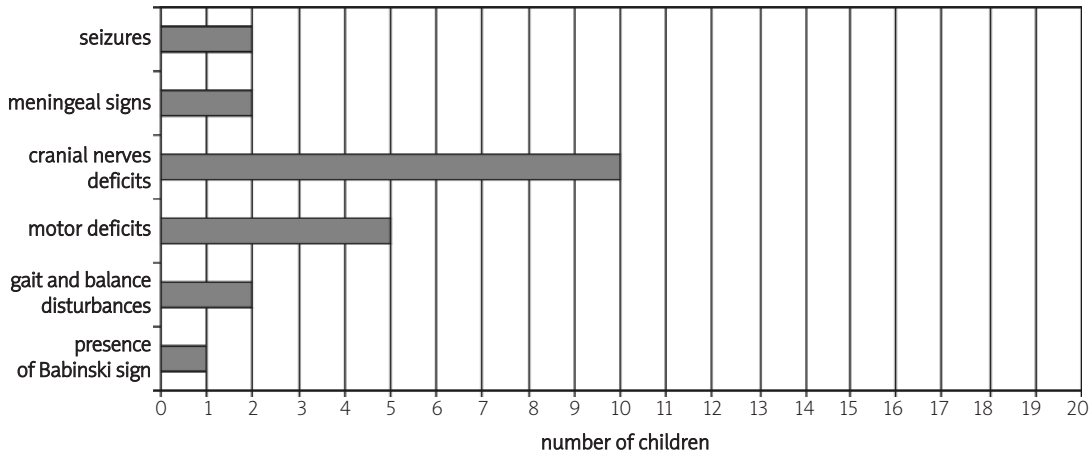

Figure 2. The incidence of particular neurological disorders in the studied population

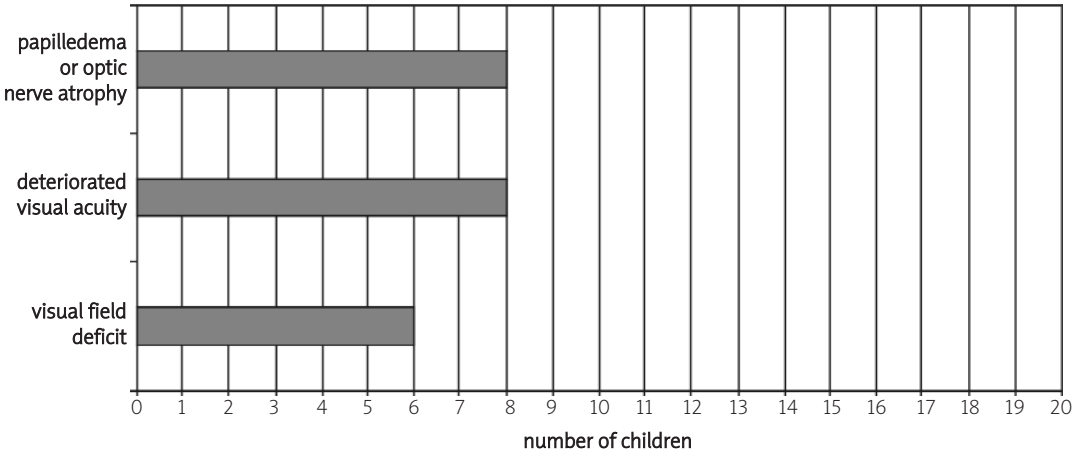

Figure 3. The incidence of particular ophthalmological disorders in the studied population

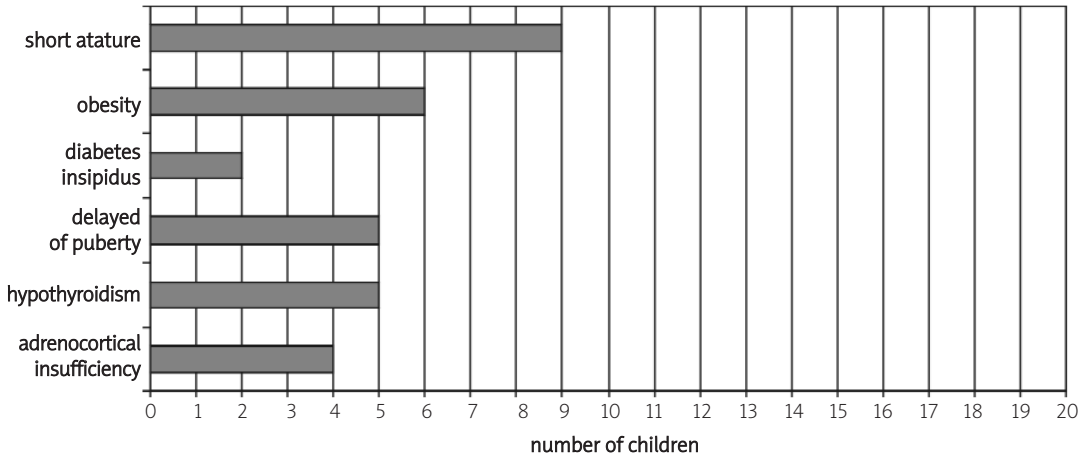

Figure 4. The incidence of particular endocrinological disorders in the studied population

parents for already 2-3 years but only in 3 of them it was the reason for the child attending the out-patient clinic. Among the other endocrinological symptoms, only DI occurrence was the cause of reporting to the doctor. The other disorders were not diagnosed until medical examinations, preceding directly the surgery, were performed.

Evaluation of CT or MRI examinations

Regarding our material, in 9 cases, the tumour was localised in the *sella turcica* and in the suprasellar region, while in the other 10 cases it was only growing in the suprasellar region. In 9 cases, the tumour indented into the III ventricle and in other 6 – it dislocated the optic chiasm. In 1 case, the tumour occupied the frontal, the parietal and the temporal lobe. In another case, tumour – together with affecting the suprasellar region – also displaced the left cerebellum peduncle, the brain stem and ventricle IV.

Brain MRI scanning, with a description of lesion structure, was performed in 14 cases revealing a cystic tumour in 9 children and calcifications – in 7 children.

Discussion

The diagnosis of CPH in children usually takes place at the age of 10-11 years [1]. A similar result was also obtained in our study. However, in 8 children tumour diagnosis was made after the 14th year of life, thus it may be assumed that – at least – in some of those cases, CPH should have been diagnosed at a younger age.

In our studies, similar to many other reports [8, 9, 10], it was found that the most frequent initial symptoms occurring in a child with CPH are headaches and vomiting (above than 60% cases). Seizures and positive meningeal signs, also resulting from the increased intracranial pressure, were found less frequently (about 5% of cases) [9].

The neurological disorders were found by us with a similar frequency as in the report of other authors [11]. The ophthalmoplegia and anisocoria were the most frequently described symptoms. An interesting

observation was the finding of nerve VII paralysis in one of the girls, which occurred twice during the year, preceding the diagnosis.

In some other reports, disorders of the visual organ were observed with less frequency than in our material [9, 10, 12], but in some of them – with greater [11]. The frequency of ophthalmological disorders in our study may vary from that reported by other authors cited above, because it depends on tumour localisation and its spreading. It should also be noted that visual disturbances may not manifest up to a certain moment because of a high resistance of the optic route nervous tissue. It is estimated that in more than 30% cases, changes within the visual organ may be irreversible considering the present potential of CPH diagnostics [13].

The most often described symptom, connected with CPH-induced hormonal disorders, is growth retardation [14]. GHD, prior to CPH diagnosis in children, is confirmed by observations of many authors and occurs with frequency from 75% to 88% cases [15, 16]. The mean SDS value of height in children with CPH before the neurosurgical treatment was evaluated by de Vries et al. [9]; it was significantly lower than the mean SDS value of the target height of children (calculated on the basis of the parents' height). In our material, short stature was found in 45% patients. However, one should be aware of the fact that growth retardation is suggested by not only the low HSDS value but also a worse centile position of the child (more than 2 centile spaces in the centile chart). Moreover, growth retardation can be recognized in case when the child's height is lower than 2 centile spaces, in comparison with the centile space of the mean parents' height. In order to evaluate the latter two parameters, it is necessary to obtain earlier measurements of the child's height and of the parents' heights. In our study, no such data were available. Therefore, the number of children, assessed as patients with growth retardation, may be underestimated in our investigation.

It has recently been proved that the growth retardation is present in all the children with CPH. The differences are related to time of the onset of the disease and they depend on the possible involvement of the hypothalamus [14].

As regards tumour localisation in our studies, no difference was found between children with short stature and those without height deficit.

In the course of growing tumour mass, the disorders of other pituitary hormones secretion occur, which has also been confirmed by us in the present study. Sklar [16] has observed that in children with CPH, ACTH deficiency in the preoperative period occurs in 25% of children, TSH deficiency – in 25% and LH and FSH deficiency – in 40%.

Among our patients no case of precocious puberty was found, even if such cases are reported in medical literature [9].

According to Khafage et al. [12], DI occurs in 36% case of CPH in the preoperative period. In our study, the symptoms of polyuria and polydipsia occurred only in 10% of cases, however, in other 3 patients hypostenuria was observed which could suggest the onset of DI in those children.

It was well known that the obesity is diagnosed in more than 50% of children with CPH, but this disease depends on the localisation of the tumour [14]. Following the data by Muller et al. [14], including 90 children with CPH, the significantly higher value of BMI SDS in the preoperative period was observed if the hypothalamic localisation of the tumour was confirmed [14]. In our group of patients, obesity was diagnosed in 30% of patients. Furthermore in our study, no differences were found, as regards tumour localisation, between the children with obesity and without this disease.

The results of our present study may be helpful for physicians diagnosing children with CPH. As far as the occurrence of neurological or ophthalmological disorders is a cause of immediate beginning of diagnostics, the incidence of some general or endocrinological disorders is usually overlooked. Moreover, it appears that, even if children with CPH are neurologically and ophthalmologically examined before the surgical treatment – endocrinological diagnostics is – in many cases – omitted. Most often, it is related to the urgent need for prompt neurosurgical intervention because of the increasing intracranial pressure. During the preoperative period, in the analysed by us group of children hormonal tests were ordered in 7 children only. It is to be recalled that, according to the majority of authors, children with suspected CPH should be submitted to the tests for secondary adrenal insufficiency, secondary hypothyroidism and diabetes insipidus, prior to the surgical treatment and this diagnostics should be followed by the respective replacement therapy, if necessary [16].

Conclusions

1. In the preoperative period, a considerable number of children with CPH, reveal functional disorders of the pituitary, manifested by growth retardation, secondary hypothyroidism and adrenocortical insufficiency.
2. The hormonal evaluation, especially of the thyroid gland and adrenal cortex, should routinely be performed in children with CPH before the surgery, due to the necessity of appropriate hormonal replacement therapy in cases of secondary hypothyroidism and/or hypoadrenia.

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