CASE REPORTS

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Brain histiocytosis with precocious puberty and growth hormone deficiency at early childhood – A case report

Histiocitoza moždanog tkiva sa preranim pubertetom i deficitom hormona rasta u ranom detinjstvu

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Abstract

Introduction. Langerhans Cell Histiocytosis (LCH) is a rare chronic granulomatous, usually multisystem disease of elusive etiology, with peak incidence in early childhood and slow progressing course. Isolated brain histiocytosis is a very rare condition and neurological finding does not correlate with the extent of space-occupying anatomical lesions and degenerative changes. **Case report.** A girl, age 2.5 years was presented with diabetes insipidus and nearly fatal full spectrum isolated brain histiocytosis. Brain magnetic resonance imaging (MRI) showed multiple nodules with perifocal edema, the most prominent in the projection of the hypothalamus/pituitary and the stalk and in the region of the pineal gland. Identical nodules were present in both caudate nucleus and putamen, left insular subcortex, both temporal lobes, tegmental area of the midbrain, central part of pons and medulla, both cerebellar hemispheres and leptomeningeal membranes. The pattern resembled snow balls and flakes. Biopsy showed positivity for vimentin, S-100, CD-68 and CD1a markers. Treatment protocol LCH-III was not successful and a salvage treatment was refused by parents. She appeared again at the age of 7 with growth deceleration and fully developed precocious puberty. The control MRI of the brain revealed similar nodules in certain regression. Due to central precocious puberty, treatment with luteinizing hormone–releasing hormone (LH-RH) analogue was introduced. School performance was mediocre with cocktail-party effect behavior and slower speech. **Conclusion.** Brain histiocytosis is potentially fatal disease with chronic, variable, slowly progressive course and unpredictable responses to treatment protocols.

Key words:
histocytosis; brain; diagnosis; diabetes insipidus; drug therapy; treatment outcome.

Apstrakt

Uvod. Histiocitoza Langerhans-ovih ćelija (LCH) je retko hronično granulomatozno multisitemsko oboljenje sporog toka i nejasne etiologije, sa najvišom incidencom u ranom detinjstvu. Izolovana histiocitoza moždanog tkiva je vrlo retko stanje, a neurološki nalaz ne korelira sa obimom anatomskih lezija i degenerativnih promena. **Prikaz bolesnika.** Opisana je devojčica uzrasta dve i po godine sa insipidnim dijabetesom, punim spektrom histiocitoze moždanog tkiva i skoro fatalnim ishodom. Magnetna rezonanca (MR) je pokazala multiple noduluse sa perifokalnim edemom u regiji hipotalamusa, stalka hipofize i pinealnoj žlezdi. Slične promene nađene su u *nucleus caudatus*-u i putamenu, levom insularnom korteksu, oba temporalna režnja, tegmentnom delu mezencefalona, medijalnom delu ponsa i medule, obe cerebelarne hemisfere i na leptomeningama, dajući sliku snežnih grudvi i pahuljica. Biopsija je pokazala pozitivitet na vimentin, S-100, CD-68 i CD1a markere. Terapijski protokol LCH-III nije dao povoljan rezultat, a *salvage* terapiju su roditelji odbili. Devojčica se ponovo javila na pregled u uzrastu od sedam godina sa deceleracijom rasta i preranim pubertetom, kada je uvedena terapija analogom "rilizing" hormona luteinizirajućeg hormona (LH-RH). Kontrolni MR snimak endokranijuma pokazao je slične noduluse u diskretnoj regresiji. Uspeh u školi je bio osrednji, govor usporen i ponašanje ekstrovertno. **Zaključak.** Histiocitoza mozga je potencijalno fatalno oboljenje hroničnog, varijabilnog, sporo progredirajućeg toka i nepredvidivog odgovora na terapijske protokole.

Ključne reči:
histocitoza; mozak; dijagnoza; dijabetes inspidus; lečenje lekovima; lečenje, ishod.

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Introduction

Langerhans Cell Histiocytosis (LCH) is a rare chronic granulomatous, usually multisystem disease of elusive etiology, most commonly affecting the bone (skull, longitudinal bones, spine), bone marrow, skin, liver, lungs and infrequently salivary glands (parotid), thyroid gland [1], gastrointestinal tract (colon, duodenum) and brain and can occur at any age, with peak incidence in early childhood. The annual incidence in children under 10–15 years is 0.2–2 *per* 100,000 children. Granulomas are composed of immature histiocytes, lymphocytes, giant cells and eosinophils. It has a slow progressing course. Isolated brain histiocytosis is a very rare condition and neurological finding does not correlate with the extent of space-occupying anatomical lesions and degenerative changes. Magnetic resonance imaging (MRI) and histopathology show changes of brain histiocytosis into three patterns [2] – infiltration of the hypothalamic-pituitary region [3], neurodegenerative changes [4, 5] in cerebellum and basal ganglia and extraaxial lesions in the meninges, choroid plexus and pineal gland. Neurological deterioration includes reflex abnormalities, gait disturbance, ataxia, dysarthria, dysdiadochokinesis, nystagmus, seizures, spastic paresis or plegia, behavioral disturbances, poor concentration, memory and attention deficit, cognitive defects, mental retardation and psychiatric disorders. When the disease is detected at an early age, severe neurological consequences may occur in early adulthood, favoring its slow progression, possible arrests and the reactivations in the course and requirement of large devastation of axonal mass (threshold), that brain cannot compensate. Endocrine disorder triad includes pituitary gland – diabetes insipidus (in 50% of cases), precocious puberty and growth hormone deficiency [6], although secondary hypothyroidism, hypogonadism and hyperprolactinemia can occur.

Differential diagnosis of brain histiocytosis covers tuberculosis, sarcoidosis, Wegener's disease (granulomatosis with polyangiitis), *cysticercosis*, *coccidiomycosis*, *cryptococcosis*, cerebrotendinous xanthomatosis, Rosai-Dorfman disease (non-progressive and self-limited sinus histiocytosis with massive lymphadenopathy) [7], Erdheim-Chester disease (polyostotic sclerosing histiocytosis) and Machado-Joseph-Azorean disease (spinocerebellar ataxia).

A subset of cases exhibit somatic activating mutations in the BRAF proto-oncogene (responsible for a protein-kinase) [8].

Causal therapy is not known – corticosteroids (prednisolone), cytostatics passing blood-brain barrier (vinblastine), cyclosporine, irradiation, retinoic acid, myelosuppressive purine analog cladribine (2-chlorodeoxyadenosine), indomethacin, immunoglobulins [9] and melatonin were applied with insufficient success. Some hope gives treatment with kinase inhibitors (imatinib, sorafenib, vemurafenib) [10, 11].

Case report

A girl was presented with nearly fatal full spectrum isolated brain histiocytosis, growth deceleration and precocious puberty. She was admitted because of polyuria-polydipsia (urine volume more than 5L/24h) at the age of 2.5 years in generally good condition, except somnolence, mild dehydration, signs of hypermobility syndrome (general laxity) and imperfect dentinogenesis. She was afebrile, heart rate 72/min, respiration rate 16/min, blood pressure 100/70 mmHg. Body weight (BW) 16 kg (90 percentile), body hight (BH) 97.4 cm (97 percentile) which was congruent with familiar tall stature; body mass index (BMI) 17.02 kg/ m^2 (50 percentile).

Patient's perinatal history was unremarkable and psychomotor development uneventful. Four months ago she had varicella and afterwards was treated for pneumonia and pericarditis. Family history was not significant.

Previous head trauma or operation (anesthesia) were immediately ruled out as a possible cause of diabetes insipidus. Renal insufficiency and diabetes mellitus were excluded quickly. There were no bone involvement and no signs of Leterrer-Siwe or Hand-Schuller-Christian histiocytosis (without exophthalmos, skin rash or "geographic skull" on X-ray) [12]. Ophthalmologist did not find papilledema at initial presentation.

Overnight water deprivation test was inconclusive between psychogenic polydipsia and partial diabetes insipidus – urine specific gravity was around 1.010 (400 mOsmol/kg) at the end of the test. Decision was made to introduce replacement treatment with intranasal desmopressin (DDAVP) 5–10 mcg daily. The fluid intake was reduced to 1.5 L/24h. She was temporarily discharged but soon hospitalized at a local hospital for vomiting and somnolence (possible water intoxication due to DDAVP overdose since sodium was low – 128 mmol/L). Upon cessation of DDAVP and fluid intake reduction, urine specific gravity raised to 1.030 (1,200 mOsmol/kg), but 36 hours later polyuric-polydipsic syndrome developed again and DDAVP had to be given.

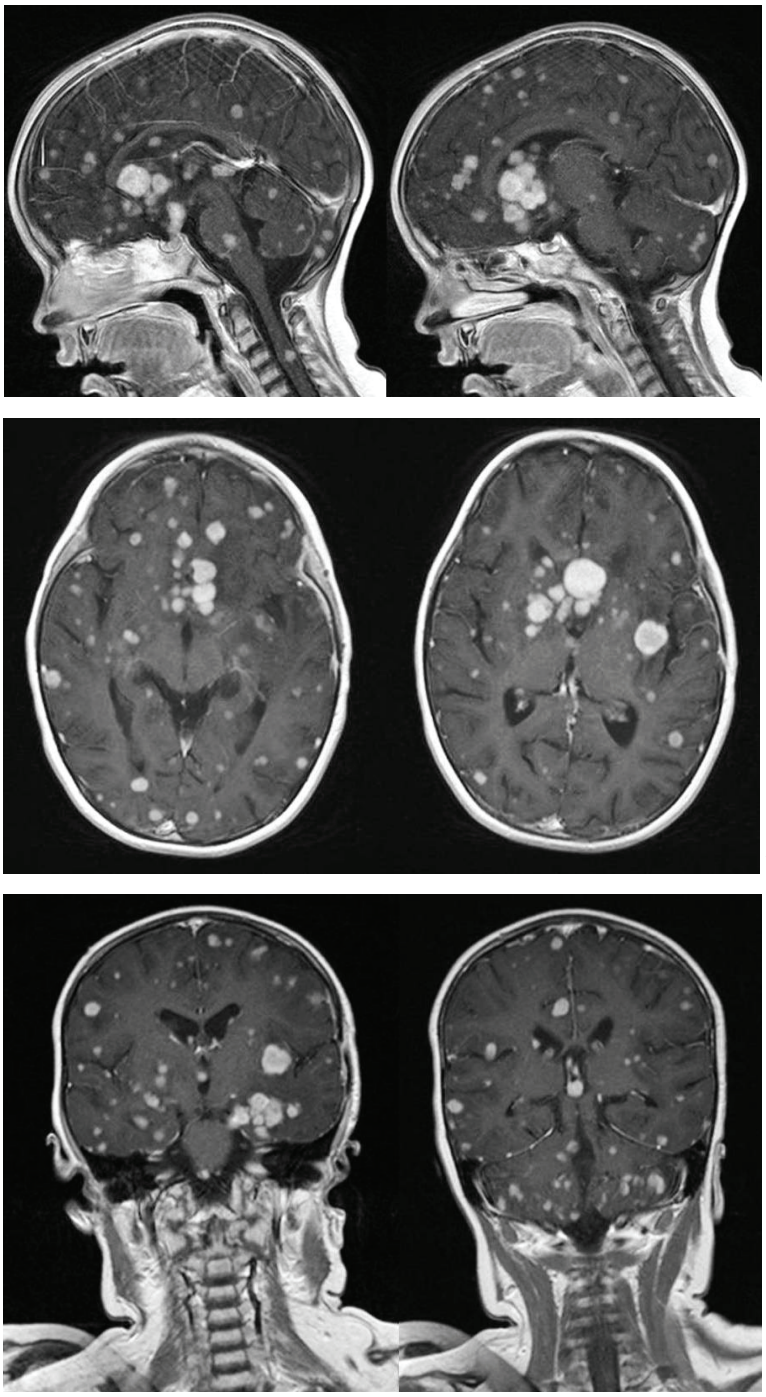
MR angiography, imaging and spectroscopy of endocranium (sagittal T1-weighted, transversal and coronal T2-weighted tomograms), accompanied with triplanar postcontrast study and detailed examination of the pituitary gland revealed multiple axial and leptomeningeal soft tissue nodules with perifocal edema, the most prominent in the medial line – in the projection of the hypothalamus/pituitary and the stalk (maximum diameter of 20 mm) and in the region of the pineal gland (15 mm) without cystic component and without calcifications. Identical intraaxial nodules were present in both caudate nucleus and putamen (8–12 mm), and in the left insular subcortex (17 mm) and in both temporal lobes (predominantly left, generating intraaxial edema). In the midbrain, one nodule in the left tegmental area was spotted, also one in the central part of pons and medulla with diameter of 3.5 mm.

In both cerebellar hemispheres were multiple nodules with diameters of 2–12 mm. At all leptomeningeal membranes (in the depths of sulci) multiple nodules of identical characteristics and genesis were found, corresponding to massive cerebrospinal fluid dissemination of the basic process; nodules generated parenchymal edema, both supra- and infratentorially. In the displayed myelin C-segment there were three micronodules with consecutive edema. Bright spot signal of the posterior pituitary gland was lost.

In conclusion, MRI showed multiple intraaxial and leptomeningeal nodules with perifocal soft tissue edema, most pronounced in the midline, and the projection of the hypothalamus, a tripod and the pineal gland. The presence of micronodules at all leptomeninges and in the projection of the displayed myelin C-segment might indicate cerebrospinal fluid dissemination of the underlying disease. The pattern resembled snow balls and flakes (Figure 1).

Disseminated nodules seen at MRI and mother's subsequent statement that she was treated for tuberculosis in the pre-conception period, tuberculosis, sarcoidosis, histiocytosis, germ-cell tumor (germinoma), Wegener granulomatosis, toxoplasmosis, neuroborreliosis, cysticercosis, cryptococcosis and coccidiomycosis came into consideration.

Cerebrospinal fluid (obtained by lumbar puncture) was under normal pressure, clear and with normal cytology, with elevated proteinorachia (0.83 g/L) and normal glycorachia and chloride level. Staining and culture techniques excluded presence of *Mycobacterium tuberculosis* in cerebrospinal fluid and gastrolavate; polymerase chain reaction (PCR) was not performed. Chest x-ray was normal and ultrasound of thorax revealed a tiny layer effusion in the left phrenocostal sinus.



a) b) c)

Fig. 1 – Brain histiocytosis: a) - sagittal magnetic resonance (MR) slices; b) axial MR slices; c) coronal MR slices.

Other mentioned pathology was also soon excluded. There were no signs of multiple pituitary deficiency – cortisol rhythm was normal (587.6–665 nmol/L in the morning and 148.3 nmol/L in the afternoon), as well as T3, T4, TSH and her height was initially adequate.

C-reactive peptide (CRP) was in the normal reference range, erythrocyte sedimentation rate (ESR) was 20, white blood cells (WBC) 8.0×10^9/L, red blood cells RBC 4.57×10^{12}/L, hemoglobin 127 g/L, hematocrit 34.9%, platelets 464×10^9 /L, fibrinogen 3.89 g/L, glycemia 5.03 mmol/L, sodium 139–145 mmol / L, potassium 4.4 mmol / L, pH 7.47 and urine specific gravity 1.010 (400 mOsmol/kg). Angiotensin-converting enzyme (ACE) activity was 526.6 nkat/L. Total serum proteins, calcium, phosphates, and alkaline phosphatase activity were in the normal range.

Tumor markers were repeatedly in the reference range: alpha-fetoprotein 4.6 IU/mL, β-HCG < 0.1 IU/L and lactate dehydrogenase, human immunodeficiency virus, hepatitis B antigen, antibodies against hepatitis C virus (LDH, HIV, HbsAg, antiHCV, respectively), direct and indirect Coombs test were negative. While C3, C4, total IgA and IgM had normal values, the total IgG was decreased 3.85 g/L (ref. range 5–13 g/L). Antinuclear, antimitochondrial, antiparietal, antismooth muscle and anticardiac antibodies were all negative. Ultrasonographic finding of the abdomen and electrocardiography (ECG) were without pathology and bone marrow biopsy revealed common pattern.

The patient underwent brain biopsy of yellowish nodules. Histopathology revealed histiocytic infiltration and immunohistochemistry proved positivity for vimentin, S-100, CD-68 and CD1a markers; *Mycobacterium* was not spotted.

Appropriate treatment protocol LCH-III (prednisolone and vinblastine) was started [13] and the child was much better soon after. Since the longterm response to the protocol was not as expected (the condition of the child deteriorated gradually with seizures, respiratory arrest, anisocoria, cyanosis and papilledema), a salvage treatment with cladribine [14] was proposed but refused by parents. After discharge, the contact was lost for a few years (parents referred to a religious pilgrimage) and the child appeared again at the age of 7 years in better condition, with BH 119.5 cm (50 percentile) that suggested growth deceleration, but with signs of fully developed precocious puberty (breasts stage 4 and recently occurred menarche), advanced bone age of 11 years, low insulin like growth factor (IGF)-1 and predictive height 135 cm only. She complained of dry mouth (anti-Ro/SSA and anti-La/SSB antibodies for Sjögren syndrome were negative).

The control MRI of the brain revealed similar nodules in certain regression. Due to central precocious puberty, treatment with LH-RH analogue was introduced. School performance is mediocre with "cocktail-party effect" behavior and slower speech.

Discussion

LCH is a rare chronic granulomatous multisystem disease of enigmatic etiology, most commonly affecting the bone, with peak incidence in early childhood. Extraosseaous involvement is rare [7], isolated brain histocytosis particularly. The most common cerebral location is the circumventricular organ [2] – pineal-hypothylamic-neurohypophyseal complex, then cerebellum, with headaches, seizures and diabetes insipidus as the main clinical manifestations, while growth hormone dificiency is the second most frequent endocrinopathy (up to 10%) [2]. It has infiltrative, space-occupying or degenerative character in brain tissue with cosequent cognitive and attention disorders [2–5]. This patient had the full clinical spectrum of brain tissue histiocytosis. Extensive pathological MRI pattern did not correlate with feeble neurological finding.

Conclusion

Brain histiocytosis is rare and potentially fatal disease with variable chronic course and slow progression. Causal therapy is not known and outcome is unpredictable.

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