Craniopharyngioma in boy suffering from chronic granulomatous disease – case report

BOŻENA POLAŃSKA 1, ALEKSANDRA LEWANDOWICZ-USZYŃSKA 1, ADAM JANKOWSKI 1, 2

13rd Department and Clinic of Pediatrics, Immunology and Rheumatology of Developmental Age, University of Wroclaw, Poland; 2 Institute of Genetics and Microbiology, University of Wroclaw, Poland

Abstract

CGD is an inherited (X chromosomal or autosomal recessive) primary immunodeficiency regarding functional disturbance of phagocytes which lead to the severe recurrent bacterial and fungal infection observed since birth. Manifestations of CGD including central nervous system are less common. This case report emphasizes the diagnostic and therapeutic problems in boy aged 18 with CGD who developed craniopharyngioma. There are no reports, to our knowledge, considering a coexistence of CGD and craniopharyngioma in children in the available literature.

Key words: chronic granulomatous disease, craniopharyngioma.

Introduction

Chronic granulomatous disease (CGD) described in 1957 by Landing and Shirkey [1] and Berendes et al. [2] is an uncommon congenital disorder affecting the phagocytic cells which are unable to generate oxygen radicals in response to catalase-positive bacteria and fungi. CGD is a very heterogeneous disorder. Several different molecular defects are known but most frequently (about 70% of cases) CGD is inherited as an X-linked recessive disease associated with mutation in CYBB gene encoding the b subunit of cytochrome b558 or gp91 and low-affinity phagocyte NADPH oxidase (phox) [3]. Phagocytic cells have abnormal intracellular microbicidal activity and persistence of microorganisms within the phagosomal vacuoles is the stimuli to a recurrent inflammatory state. CGD usually becomes apparent during the first year of life, but the diagnosis is made later. The course of this illness may be less characteristic or it can have more turbulent clinical manifestations. CGD patients have recurrent pyogenic infections involving the skin, lymph nodes, respiratory and gastrointestinal tract, liver, urinary tract, bones, and generalized infection. Changes in central nervous system (CSN) are rarely described in CGD [4-6].

The most common pathogens in patients with CGD are Staphylococcus aureus, Burkholderia cepacia, Aspergillus sp., Nocardia sp., Candida sp., Serratia sp. The second characteristic sign of CGD is granulomas formation that develops in response to a chronic inflammation which may cause obstruction of organs’ lumens and second failure of tissues [3].

Conventional therapy and prevention of infections include administration of antibiotics and antifungics. Long-term prophylaxis against infections with trimethoprim/sulfamethoxazole and itraconazole, sometimes combined with subcutaneous administration of interferon-gamma, is recommended [7]. The corticosteroid therapy is reserved for serious and obstructive conditions in CGD [8]. In serious cases the transfusion of allogeneic granulocytes may be necessary. CGD is on the list of diseases to be treated with the stem cell transplantation and the gene therapy [9, 10].

Craniopharyngioma (CP) is a rare (1.3 per million person years), intracranial neoplasm, but it is also the most frequent (about 10% of all CNS tumors) sellar tumor of childhood [11]. It is the benign epithelial tumor derived from embryonic remnants of the structures that give rise to pituitary gland, Rathke’s pouch. CPs are slow-growing, usually well circumscribed but locally invasive and may infiltrate into the brain structures. The pathogenesis is unclear. Sarubi et al. examining adamantinomatous craniopharyngiomas have not found the somatic mutations within three genes - Gsalpha, Gi2alpha and patched (PTCH) and they suggest that a subsets
of craniopharyngiomas are monoclonal and therefore are probably due to the acquired somatic genetic defects [12]. Rickert et Paulus suggest that chromosomal imbalances are a rare event in both adamantinomatous and papillary craniopharyngiomas [13]. Dysregulation of the Wnt signaling pathway may play an important role in the molecular pathogenesis of adamantinomatous craniopharyngiomas [14]. The data indicate on the significance of nuclear/cytoplasmic expression of beta-catenin and mutation of the beta-catenin gene in CF. Abundant mutations of b-catenin gene contribute to the structural abnormalities and the development of the tumor [15]. The tumor mainly involves the sellar and suprasellar regions, with calcification in 50% of these cases, whereas infrasellar is rare. There are two histologic types-adamantinomatous and squamous papillary [16]. In CT exam may be cystic (in 85% of cases), solid or mixed.

Total excision of CP is difficult because the tumor mass is situated near the suprasellar neurovascular structures and infiltrates into the hypothalamus and the optic apparatus, which can generate considerable morbidity and mortality. Some complications appear in connection with tumor location, infiltration surrounding neurovascular structures and with usually subtotal removal with following local irradiation. Most common disturbances are hypothalamic-pituitary axis with high incidence of diabetes insipidus and hormone deficits as well as visual disorders. Tumor may extend into the third ventricle resulting in obstructive hydrocephalus. Also a large number of recurrences have been reported [17, 18]. Tumor location is a significant clinical predictor of recurrence. Kim et al. in retrospective study described that the 5-year recurrence-free survival rate was 39% for those who had an intrasellar tumor component and 81% for those who did not (p < 0.05) [19]. The survival is higher among children and has improved in recent years [11].

In our study we present a boy with craniopharyngioma complicating CGD. This case is based on our own observation and patient’s medical documents.

Case presentation

The subject of our study – a 18-year-old boy was admitted to our clinic at the age of 5 due to a recurrent pyogenic infection and suspicion of the immunologic disorders.

The boy was born in July 1990 to a 29 year old mother and 34 year old father, via a vaginal delivery after a full-term and normal course of pregnancy. His body weight at birth was 3500 g, and height – 58 cm, Apgar score – 10. No complication during pregnancy, birth, and neonatal period was observed. The psychomotor development in infancy and childhood was normal. The mother of the subject was treated during the first year due to thoracic phlegmon caused by *Staphylococcus aureus* with excision part of the rib. She also has leukopenia with clinical signs, and is known to be a carrier of CGD. The boy’s father is suffering from diabetes mellitus (since 1996), vitiligo (since 2005), genetic investigation of CGD carrier-state – negative. The boy’s three sisters aged 25, 20, 15 (1982, 1987, 1992), are healthy and are not the carriers of CGD.

The patient’s infancy and early childhood course was complicated by abscesses of cutis and infection of the upper respiratory tract, mainly angina and lymphadenitis coli. At the age of 3 (June 1993) he was admitted to the regional hospital where liver abscess was diagnosed and surgical intervention was performed. Recurrence of liver abscess was observed again three times. Additionally, at the age of 4 pyocalix superior ren dexter was detected.

Patient’s life-long history of diseases is summarized in the Table 1.

On admission to our clinic (October 1995), at the age of 5, patient was well-developed, well-nourished and in a good general condition. Physical examination showed the presence of skin abscesses, chordeolum of the right eye, and cervical lymphadenitis. On the basis of the clinical history of recurrent infections, of differentiation diagnostics and decreased respiratory burst of granulocytes in chemiluminescence test we suspected a primary immunodeficiency – CGD. Final diagnosis of X-linked CGD was established by the genetic detection at the CYBB locus. When the diagnosis of CGD had been established, typical long-term prophylactic treatment with trimethoprim-sulfamethoxazole (TMP-SMX) and first ketoconazole and then itraconazole was administrated. We also used bacterofagotherapy against *Staphylococcus aureus*, the most often encountered pathogens responsible for the infections, in prophylactic treatment. After this treatment we observed significant reductions of infection and number of hospitalizations in our patient, nevertheless some complications occurred.

The patient had been treated several times in the clinic since 1995 (Table). Perirectal abscess at the age of 5.5 and recurrent cervical lymphadenitis at the age of 6 were diagnosed. What is more, a recurrent cervical lymphadenitis was diagnosed. At the age of 7 (September – December 1997), he had severe pleuropneumonia sinistra and additional interferon-gamma therapy was commenced. When serious infections occurred we used a high dosage of wide-spectrum or in accordance with antibiogram results intravenous antibiotics.

During each patient’s stay in the clinic laboratory examinations were performed. Blood tests showed an elevated red blood cells (RBC) sedimentation rate (30-40 mm/hour), leukocyte count within laboratory standards, serum hemoglobin concentration slightly decreased, elevated C-reactive protein (CRP). Other blood tests including liver and renal screen, autoimmune screen were all negative.

One year later, in December 16, 1998, our patient was admitted to the hospital because of sudden presentation of neurologic symptoms – numbness of left hand and impossibility of holding a spoon, disturbance of speech and stiffness of tongue, headache. He had no fever and vomiting. Laboratory testing on admission indicated RBC sedimentation rate –20 mm/hour, white blood cell count – 3400/µl, mild
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Anemia (hemoglobin was 11.5 g/dl), normal levels of C-reactive protein. Electrolytes, concentration of glucose, liver and kidney tests showed normal results. Blood cultures were negative. The neurologic examination on admission showed a central left side facial nerve (VII nerve) palsy, decreased muscle tone of extremity, locomotors ataxia, positive left side plantar reflex. During an ophthalmologic examination his pupils were equal and reactive but bilateral papilledema was found. The computed tomography scan of his head performed a few hours after the onset of neurological symptoms, showed a large (7 cm × 5 cm) and well circumscribed with partial calcified external capsule tumor. It was located in right hemisphere of brain in temporo-suprasellaris area. The change was described as old abscess. The patient was immediately referred to the Neurosurgery Department for further diagnostics and treatment (December 1998 – January 1999). Neurosurgical procedure involving trephinopuncture with instant drainage of abscess was performed. Simultaneously, he was receiving a wide-spectrum of intravenous antibiotic medication and antimycotic treatment. Microbiology and histologic examinations of abscess specimens were negative. After the drainage his neurological status was normal. During the next month, his visual acuity and fundoscopic changes improved markedly. Regression of the changes, visible in subsequent CT examinations, was obtained.

After 4 months (April, 1999) and then after one year (December 1999) from the first neurological signs the next

Table 1. The life-long history of CGD boy’s diseases

<table>
<thead>
<tr>
<th>Age [years]</th>
<th>Diseases</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Recurrent skin abscesses</td>
</tr>
<tr>
<td>2</td>
<td>Recurrent upper respiratory tract infections, cervical lymphadenitis</td>
</tr>
<tr>
<td>4</td>
<td>Left submandibular lymphadenitis (10.1994) Left gonarthritis (10.1994)</td>
</tr>
<tr>
<td>8</td>
<td>Brain abscess (12.1998 -01.1999; 04.-05.1999)</td>
</tr>
<tr>
<td>10</td>
<td>Aphthous stomatitis. Right sublingual gland sialadenitis. Submandibularis and cervical lymphadenitis (10.2000) Bilateral pneumonia (23.04.-08.05.2001)</td>
</tr>
<tr>
<td>11</td>
<td>Recurrent of right hemisphere brain abscess</td>
</tr>
<tr>
<td>12</td>
<td>Brain tumor (craniopharyngioma). Polyhormonal hypopituitarism (06.-07.2002)</td>
</tr>
<tr>
<td>13</td>
<td>Skin granulomas (07.2003) Bacteriemia (Staphylococcus epidermidis MRSE) (10.2003)</td>
</tr>
<tr>
<td>15</td>
<td>Gingivitis (10.2005) Bacteriemia (Streptococcus sp., Micrococcus sp.), Urinary tract infection (Enterococcus faecalis) (02.2006-03.2006)</td>
</tr>
<tr>
<td>16</td>
<td>Pharyngitis (Staphylococcus aureus) (08.2006) Chronic colitis. Anal fissure (12.2006) Skin granulomas (01.2007; 03.2007)</td>
</tr>
<tr>
<td>17</td>
<td>Cholecystolithiasis. Chronic proctitis (12.2007)</td>
</tr>
</tbody>
</table>
CT were performed and the recurrence changes at the same place were observed. Another surgical drainage of brain abscess was done. The neurologic examination on admission and after the drainage was normal.

The bacteriological examination of fluid aspirated from abscess was negative and the cytology did not reveal atypical cells (macrophages, neutrophils and eosinophils were found). This time he received maintained antibacterial and antifungal prophylaxis. Regular neuroimaging follow-up detected abscess recurrence was carried out.

At the August 2001, an ophthalmologic examination revealed the right hemianopia, normal fundus of both eyes, no signs of stasis. This time he continued receiving antibacterial and antifungal prophylaxis and systemic steroids and periodic intravenous application were added. The patient was maintained under periodic control. He had no neurological signs and his vision improved. No new changes in the MR were noted.

After a period of noncompliance at the age of 12 (June, 2002) in the control MRI of the head progression changes appeared and the patient was readmitted to the Neurosurgery Department. Findings of physical examination on admission were normal except for the signs of iatrogenic Cushing syndrome (post steroid treatment). The neurologic examination was normal but in ophthalmologic exam impairment of visual acuity, and bilateral optic atrophy were found. A MRI (Fig. 1) demonstrated a large (9 cm × 6 cm × 4,5 cm), irregular, sharply separated tumor. It was mixed – solid-cystic with numerous amorphous calcification. It was located in sellar and suprasellar area and penetrated into the base of both (right and left) frontal and right temporal lobes. It was extending into the posterior cranial fosse and below, with the left side predominance, compressing the trunk of brain. In superior part it was extending into the third ventricle, pressing frontal horn of the left lateral ventricle of the brain and head of caudate nucleus.

The patient underwent bilateral subfrontal craniotomy (Luly, 04, 2002) with a partial excision of tumor. A histologic examination confirmed the diagnosis of craniopharyngioma. His postoperative course was good but he temporarily developed unstable diapedes insipidus, hypoglycemia and sixth left nerve paralysis. His visual deterioration was stronger in the right eye than in the left eye.

After the surgery, the conformational radiotherapy consisting of a total of 5400 cGy (30 fractions), for residual tumor was administered one month later. The boy was discharged home in good general condition, with signs of bilateral optic atrophy and pituitary dysfunction without other focal neurologic signs. Supportive hormone therapy (levothyroxinum) was commenced. Moreover, a typical prophylactic treatment in order to minimize bacterial and fungal infections (trimethoprim/sulfamethoxazol and itraconazole) was continued.

A clinical follow-up after a partial surgical excision (removal of the brain tumor) of craniopharyngioma by bacteremia (Staphylococcus epidermidis MRSE, Streptococcus sp, Micrococcus sp.) and recurrent nonulcerating cutaneous granulomas was complicated (table). Due to the fact that stool was positive for blood he was referred to the Gastroenterological Department (2006) where chronic colitis, anal fissure was diagnosed and the treatment with mesalazine (rectal suspension and suppository) was instituted. In 2007 during the routinely ultrasonography controlled choleliths in cholecyst, without abdominal symptoms, were found.

Because of the symptoms of pituitary dysfunction (low growth hormone, thyroid-stimulating hormone, gonadotropin secretion) the patient received a substitution therapy (levothyroxine, testosterone).

At present, 6 years after the diagnosis of craniopharyngioma, the patient is in good clinical condition. His actual physical examination: mild obesity and stunted growth (height and weight is below the 3rd percentile), with normal proportions, skeletal maturation, assessed by bone age determination, <3 year behind chronologic age, delayed pubertal development. On ophthalmologic exam the patient is noted to be blind in his right eye, with ptosis of his right eyelid, and his left eye’s visual fields revealed a lateral hemianopsia. The psychological status of boys is good.

Routine biochemical assessment of blood (e.g. complete blood cell count, total serum protein, albumin and globulin levels, concentration of glucose, parameters of liver and kidney function, electrolytes with iron level) was normal. Additional investigations such as LDH, CPK, alpha-fetoprotein (AFP) level, showed normal results. Erythrocyte sedimentation rate and C-reactive protein were usually 2-3 times higher than the normal range, both in inflammation state and in period when no signs of disease appeared. Simultaneously, the plasma level of neutrophil elastase with
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Fig. 2. Postoperative (May, 2007, 5 years after the brain tumor excision) of head MRI
α₁-protease inhibitor complex (ELISA test) in acute state of diseases was elevated above norm. The serum Aspergillus and Candida antigen investigated several times (by ELISA and PCR methods) was always negative. The HIV 1/2 and CMV IgG and IgM antibodies were negative, EBV IgG was positive and EBV IgM was negative.

We observed periodically lower serum concentration of IgG, IgG3, IgM, mildly elevated total IgE, presence of circulating immune complexes. Since 2006 immunological disorders in subpopulation lymphocytes T (decreased CD3, CD4, and CD8, consequently the ratio of CD4 to CD8 was decreased), decreased NK cells, and elevated CD19 were found. Other immunological tests (including hemolytic activity and concentration C3 and C4 of complement, total value of phagocytic activity, blastic transformation of lymphocytes T after stimulation with PHA and Con A, ANA) were normal or negative.

In the control MRIs (performed every 6 month) not only progression of the tumor but also its slight regression is observed (Fig. 2).

Also, no deterioration in visual changes is observed. The patient slowly grows and the secondary sex characters are observed. He receives a long-term prophylaxis against infections trimetoprin/sulphametoxasol and itraconasole, appeared. He represents a 23-year-old CGD male. In this case post mortem characteristic pigmented macrophages contained fine, golden-brown, lipofuscin-like material were found [21]. In the available literature we found only individual cases of brain abscesses in CGD patients [20, 22].

Discussion

We describe a boy, 18 years old at present, who suffered from CGD since early infancy and who developed a craniopharyngioma 3 years after the surgical drainage for recurrent brain abscesses. Our patient represents, to our knowledge, the first reported case of craniopharyngioma complicated CGD.

Although CGD is a rare primary immunodeficiency (1 case in 220 000-500 000 live births), it creates serious clinical problems connected with recurrent serious infections, long – term therapy and in most cases with bad prognosis and high mortality. Analysis of the data indicate that both morbidity and mortality rates are higher in X-linked form CGD, which our patients represents. A substantial number of patients died during the second and third decade of life. Diagnostic and therapeutic problems may arise because of unclear clinical symptoms, difficulty in isolating a causative organism and variety of changes in radiological examination [20]. Changes in the CNS may be e.g. interpreted as multiple sclerosis (MS) as Hadfield at al. described in the case of a 23-year-old CGD male. In this case post mortem characteristic pigmented macrophages contained fine, golden-brown, lipofuscin-like material were found [21]. In the available literature we found only individual cases of brain abscesses in CGD patients [20, 22].

Primary immunodeficiencies have many clinical manifestations. The risk of developing these diseases and complications is affected by various factors (e.g. – age, sex, race, and exposure to environmental agents). The affected patients are at risk for the autoimmune/rheumatologic disorders and may also develop cancers [23, 24] but the pathophysiological processes contributing to these complications are poorly understood.

The data suggest that neutrophils in CGD patients are more resistant to spontaneous apoptosis and abnormal clearance of apoptotic cells [25] and during phagocytosis neutrophils and macrophages produce significantly less anti-inflammatory mediators such as prostaglandin D(2)(PGD2) and transforming growth factor-beta (TGF-beta) [26]. Those facts may contribute to the persistence of inflammation and the occurrence of sterile complications.

Also in CGD patients the elevated concentration of both proinflammatory cytokines [interleukin-8 (IL-8), interleukin-10 (IL-10)] and anti-inflammatory cytokine [interleukin-10 (IL-10)] were found. This disturbance may contribute to the increased susceptibility to invasive pathogens [27, 28]. Additionally, IL-8 is known as a potent chemoattractant for neutrophils and its elevated concentration in CGD may raise influx of neutrophils into inflammatory focus and contribute to the creation of a vicious circle and support the inflammation.

Polymorphism in genes regulating the immune response plays a very important role in modifying signs of the disease. Foster et al., investigating the genetic modifiers of CGD, found that a higher risk for autoimmune/rheumatologic complication occurs in patients with mannose binding lectin (p = 0.01), both mannose binding lectin and Fc gamma receptors IIa (p = 0.003), and is weakly associated with an Fc gamma RIa genotype (p = 0.04) [29].

Both in autoimmune diseases and in neoplasms, the immune system is impaired and damaged so that it cannot prevent immune cells from responding to stimulation by self-antigens and destruction of foreign bodies, e.g. cancer cells.

The etiology of cancer remains unclear. It is well known that overproduction of reactive oxygen species and nitrogen species may play a key role in carcinogenesis [30]. On the other hand, they can induce apoptosis and may serve as cancer preventive agents. It is possible that in our patient the lack of ROS did not stopped the development of craniopharyngioma. Among inflammatory causes, the human herpes virus, Epstein-Barr virus (EBV), is known as a virus that is associated with cancer disease especially with Burkitt’s lymphoma (BL), nasopharyngeal carcinoma, and also lymphomas arising in patients with immune dysfunctions [31]. Although our patient had positive EBV IgG antibodies, the probability of any connection between CGD and CP is very difficult to be defined.

The coexistence of CGD and cancer is uncommon. In 1977 O’Regan et al. described a 5-year child suffering from myelogenous leukemia although the initial signs suggested
Conclusions

A coexistence of CGD and craniopharyngioma determines a significant health problem. On the basis of our case we suggest that the precise molecular investigation is necessary to understand the pathophysiology of both CGD and CP. In this case a systematical, precise physical and psychical examination, repeated laboratory investigation with imaging findings, the continuously administration of medicine, and multidisciplinary management prove to be very important. Such action should early detect serious complication as well as it should improve the quality of life and survival rate.

Acknowledgements

Written consent was obtained from the patient and their parents for publication of patient’s clinical history.

Competing interests

The author(s) declare that they have no competing interests.

References