



# PULMONARY ASPERGILLUS IN PEDIATRIC PATIENT BY CT

## ASPERGILOSIS PULMONAR POR TOMOGRAFÍA COMPUTARIZADA EN EL PACIENTE PEDIÁTRICO

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### KEY WORDS (MeSH)

Aspergillosis

Tomography

Lung

### PALABRAS CLAVE (DeCS)

Aspergilosis

Tomografía

Pulmón

### SUMMARY

Pulmonary aspergillosis is a mycotic disease with many manifestations which depend on the immunological state. The purpose of this article is to show the different forms of aspergillosis in children. The radiologist plays an important role, especially in early detection with the invasive forms of immunosuppression, due to prognostic implications.

### RESUMEN

La aspergilosis pulmonar es una micosis con un espectro variable de manifestaciones que dependen del estado inmunológico. El propósito de esta revisión es mostrar las diferentes modalidades de la aspergilosis en los niños, en las que el radiólogo cumple un papel importante, especialmente para la detección temprana de las formas invasivas en inmunosupresión, debido a sus implicaciones pronósticas.

### Introduction

The resulting effects of exposure to fungi are diverse and amply documented. The clinical manifestations of infections due to fungi vary from mild symptoms, such as headache and allergy, to pulmonary invasive infections and infections of the central nervous (1,2). According to a study of autopsies between 1989 and 2003 in patients with hematological diseases and invasive mycosis, the prevalence of invasive mycosis has increased from 19 to 25% (1); between 50 and 88% of invasive forms are diagnosed post mortem (1,2). In 20-30% of atypical patients, most fungi that cause respiratory illness are present in 2 to 10  $\mu\text{m}$ , which eases their entry to the respiratory system, causing rhinitis, asthma, and bronchopulmonary mycosis (3).

Most pediatric publications supply information regarding several conditions, such as associated pulmonary aspergillosis with cystic fibrosis, allergic bronchopulmonary aspergillosis, granulomatosis and invasive forms. (4). These invasive forms have emerged as an important cause of morbidity and mortality in pediatrics. Their incidence has increased by about 14 times in the last years, due to an increase in immunosuppressive therapies (5); therefore, the most affected organs in order of frequency, are: lungs (70%), skin (20%), central

nervous system (brain, spinal cord), and sinuses. (18%) (6-8). In cases of spinal medullar involvement, it may be preceded by aspergillosis spondylitis; however, aspergillosis spondylitis is a condition which is quite rare (9).

### Definition

Pulmonary aspergillosis includes a group of mycotic diseases with an important angiotropism, given by species *Aspergillus* sp., which is an ubiquitous fungus in the environment which saprophytically lives in vegetable remains (3), cereal grains, organic materials which is decomposing, fertilizer, plants, air conditioning, walls or ceilings in humid places, bathroom curtains, old rugs. Their most common subtypes are fumigatus, flavus, and terreus (4,5,10) (figure 1).

### Clinical manifestations

The manifestations of *Aspergillus* depend on the immunological status of the patient, in such a way that these change depending on whether the patient is immunologically competent or immunologically suppressed. Immunologically competent patients can be separated into two groups, those with some type of pulmonary structural damage, such as a cavitation, and those who

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suffer from an associated illness such as asthma, cystic fibrosis, allergy or a chronic granulomatous disease (6). Those in the first group (with structural damage) may suffer from chronic pulmonary aspergillosis, with or without presence of an aspergilloma, or suffer simply from isolated aspergilloma. Those patients (with associated disease) commonly suffer from the disease called allergic broncho-pulmonary aspergillosis.

On the other hand, patients with immunosuppression mainly suffer from invasive aspergillosis, which is life-threatening if not treated early. This disease must receive the most attention (11). Table 1 summarizes the spectrum of grouped pulmonary aspergillosis, in non-invasive and invasive forms.

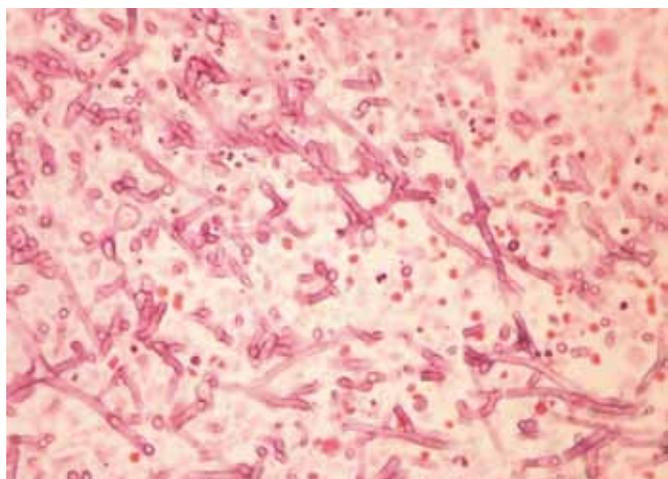


Figure 1. *Aspergillus* hyphae: Septated morphology hyphae are observed with diameters that vary from 3-6 microns, and are ramified in 35-45 degree angles (H&E).

Table 1. Spectrum of pulmonary aspergillosis

Non invasive	Invasive	
Aspergilloma with/without chronic aspergillosis	Semi-invasive	
		Angioinvasive
Allergic broncho-pulmonary aspergillosis	Invasive	Aeroinvasive

## Aspergilloma

Associated with a pre-existing cavitation, caused by a different disease such as tuberculosis, sarcoidosis, bronchogenic cyst, lung sequestra, or a secondary pneumotacele to an infection by *Pneumocystis jorveci* in AIDS patients. Computerized tomography (CT) usually shows a solid or oral mobile image within a cavity, where increased air flow sign can be identified (12,13) (figure 2). The prevalence of aspergilloma according to geographic area varies from <1:100,000, such as in the USA and Western European countries, until 42.9:100,000, as is the case in the Republic of Congo and Nigeria (14). Treatment varies according to the clinical condition of each case, and a spontaneous resolution is informed only in 10% of cases.

Lobectomy is justified when there a risk of life-threatening hemoptysis, as long as the patient has a good pulmonary reserve, allowing a therapeutic success between 85 and 100%. In cases of insufficient pulmonary reserve, the alternative is to remove the ball of fungus along with thoracoscopy. In case of significant hemoptysis, the em-

bolization of the bronchial or intercostal arteries is the recommended management. Anti-mitotic medical treatment has not shown a benefit in aspergilloma (12,15).

## Allergic broncho-pulmonary Aspergillosis

It has an incidence of 20% in cases of asthma (16), and a prevalence of 7.8% in cystic fibrosis (17). It is characterized by the affectation of pulmonary function (18) and cause inflammation (19), associated to the presence of mucus that contains eosinophils, fungi and protein D which comes from pulmonary surfactant. The latter one is also elevated in serum (20-22). Allergic broncho-pulmonary aspergillosis (ABPA) is the result of a type I complex hypersensitivity reaction, followed by type III, where the inflammatory cells are deposited in the bronchial wall, damaging it and provoking bronchiectasis. Rosenberg and Patterson criteria are used for diagnosis, which include clinical, immunological and radiological findings, as shown in table 2 (15).

Table 2. Rosenberg and Patterson Criteria

Main criteria
Bronchial asthma
Hyper-sensitivity reaction immediate to the <i>Aspergillus</i> antigen
IgE serum reaction > 1,000 UI/ml
Specific IgG for <i>Aspergillus</i> antigen, and duplication of IgE levels in respect to the average value, plus two standard in cases of asthma due to hypersensitivity to <i>Aspergillus</i> .
Central bronchiectasis through TACAR.
Serum precipitins against <i>Aspergillus fumigatus</i>
Fixed or floating pulmonary in the thorax radiography.
Eosinophils in peripheral blood > 1,000 cells / $\mu$ l
Minor criteria
Sputum cultures which show growth of <i>Aspergillus</i>
Expectorated mucus plug of a grey-blackish color.
Type III cutaneous reaction to <i>Aspergillus fumigatus</i>

In a CT scan, 2-3 cm long and 6-8 mm diameter homogenous opacities in “glove finger” and in “dental paste” shapes can be seen in the active status of the disease, which are the result of the presence of mucus in the airway which predominates in the superior lobes. Similarly, in the active form, “railway” shaped images can be seen, which consist of parallel lineal shadows which leave from the pulmonary hilum to the periphery. Their length is equal to the width of the bronchi. These railway images represent the peribronchial inflammation in the absence of intrinsic damage to the bronchi wall. In addition, levels of liquid air and perihilar opacities can be identified, due to detritus or liquid collections.

The chronic status is associated with central bronchiectasis which is also defined as “railway” images or “ring-shaped” images (figure 3). Lately, it has been suggested that the two CT categories are actively divided, according to the density of the mucus in respect to the density of the paraspinal muscles. The first category, which has a greater density to the muscle, is related to an active disease and a greater risk of recurrence; the second category, which has equal density to the muscle, has a low risk of recurrence (15).

## Semi-invasive Aspergillosis

It is also called necrotizing chronic bronchitis. This type of aspergillosis has a necrosis and granulomatous inflammation of the bronchi,

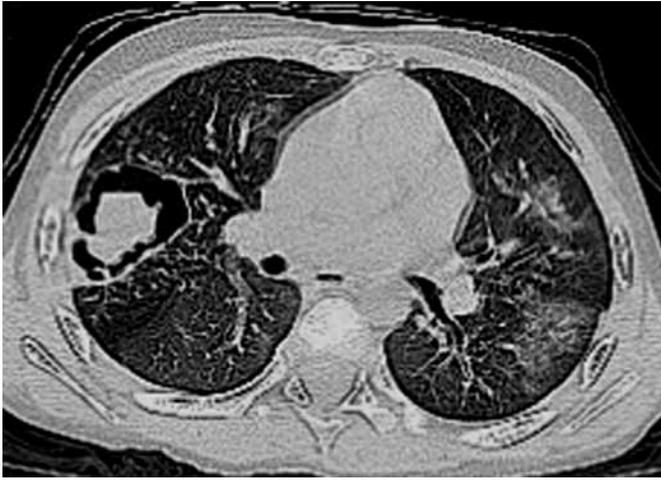


Figure 2. Aspergilloma: TACAR of the patient with a history of bronchogenic cyst, which shows a cavity of thick walls and intra-lesion mass of the pleural base.

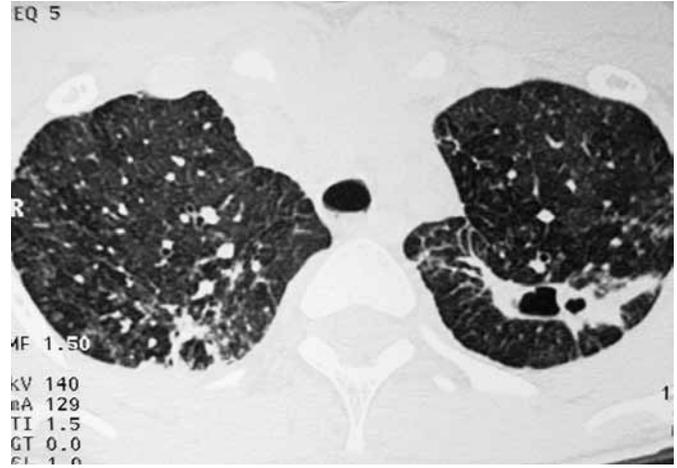


Figure 4. Semi-invasive aspergillosis. 10-year old patient with a history of malnutrition, coughing and hemoptysis with a five-month evolution. The CT scan shows a consolidation image of the left superior lobe with associated cavitation.

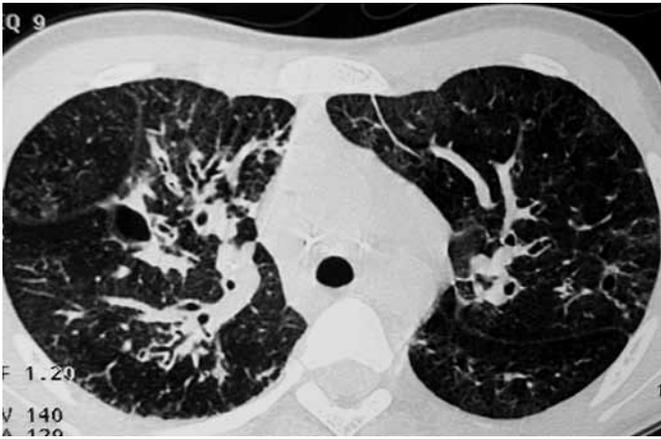


Figure 3. 8-year old boy with a background of asthma, persistent coughing, where the TACAR shows some central bronchiectasis in the superior lobe, as well as areas of thickening of the pulmonary interstice in a patient with allergic broncho-pulmonary aspergillosis.



Figure 5. Early stage angioinvasive aspergillosis. Characterized by a CT scan by nodes with perilesional "frosted glass" halo, in a 6-year old girl with diagnosis of LLA and febrile neutropenia.

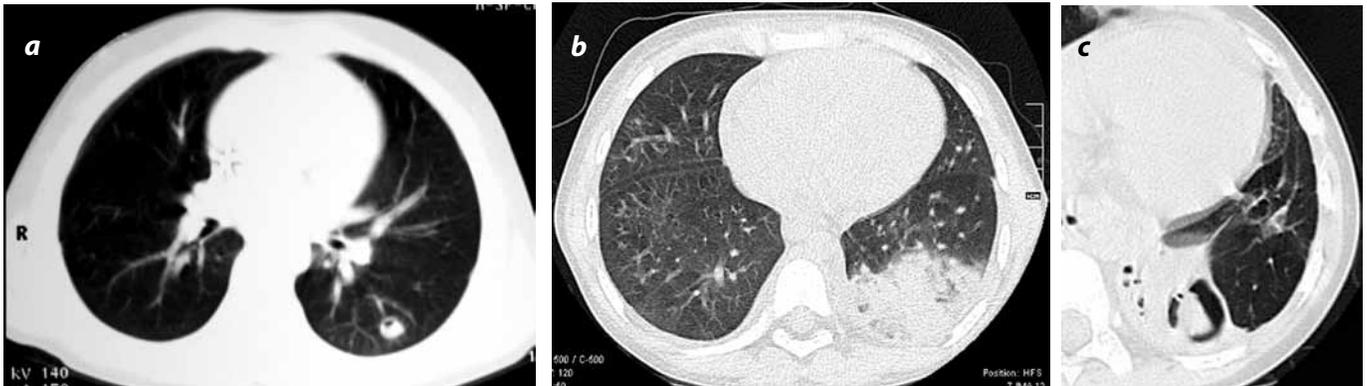


Figure 6. Latter stage of angioinvasive aspergillosis: (a) TACAR which shows a cavitated node in a 6-year old patient who is undergoing lymphoma treatment. (b) consolidation in a 3-year old boy with a bone marrow transplant and severe neutropenia, where the TACAR shows a consolidation area of the left superior lobe. (c) Increased airflow sign in a 9-year old patient with acute invasive aspergillosis in a phase of convalescence which simulates an aspergilloma (pseudoaspergilloma). Pulmonary Aspergillosis by computerized tomography in the pediatric patient.

similar to the reactivated TBC. It is associated to chronic debilitating injuries, such as diabetes, malnutrition, alcoholism, consumption of marijuana, and use of corticoids. Through CT scans, unilateral or bilateral images of pulmonary consolidation can be seen, with a presence or non-presence of cavitation and adjacent pleural engrossing, or several high-density pulmonary node areas (11,12,22) (figure 4).

### Invasive Aspergillosis

Several studies of children and adolescents who have been treated for cancer have shown that 65-75% of them suffered from invasive aspergillosis. Their rate of fatality can range from 69-89%; the risk of death increases fivefold when deep tissues are compromised (5,23-25). Children at risk of invasive forms are associated with factors exposed in table 3 (5).

**Table 3. Risk factors**

Newborns and babies with low birth weight
Children with primary immunodeficiencies. Defects in the phagocyte system of the host.
Acquired immunodeficiency Cancer treatment Marrow failure syndromes Allogeneic transplant of hematopoietic mother cells Solid organ transplant
HIV advanced infection
Immunosuppression therapy
Acute disease or trauma
Chronic lung disease

The neoplasias which are most related to invasive forms are the lymphohematopoietic system neoplasias, with an incidence of 3.7% for acute myeloid leukemia, 0.6% for acute lymphoblastic leukemia, 0.4% for lymphoma, 0.3% for high dosage chemotherapy with rescue through mother cells and 0.1% of solid tumor transplants, based on the 2000 database for US children. The allogeneic transplant of mother cells is also frequent, with an incidence of 4.5% for an in-hospital mortality of 45%, and an attributable mortality of 34%, according to the same database (6). Regarding the solid organ transplant, aspergillosis is less frequent, with a rate of 6 in 1,593 solid organ receptors, and a post-transplant incidence of 5% for the lung, 0.5% for the liver, and 0.3% for the heart (5,26).

The angioinvasive form is also present in patients who are immunologically compromised, as is the case in severe neutropenia (PMN > 500), chemotherapy of solid tumors, lymphomas which imply a difficult treatment, myelomas, resistant leukemia and functional neutropenia by steroids. Its early detection is key in order to change the prognosis and to perform the treatment with caspofungin, amphotericin B or both (27-31).

Given that in these cases, the culture does not permit rapid diagnosis, the immunoassay of serum samples or bronchoalveolar lavage is used in order to detect fungi antigens (complex carbohydrates of the walls), such as galactomannan, with a sensitivity of 89% and a specificity of 92% (32, 33), and 1,3- $\beta$ -glucan, which is

less specific for *Aspergillus*, but has a sensitivity of 55-100%, and a specificity of 71-93%. These methods may also be used in cases of immunocompetence (5,33-44).

A study performed in 36 pediatric patients in Hospital de la Misericordia, a galactomannan with a cut-off point of 0.5 in optic density, had a diagnostic sensitivity of 92% and a specificity of 100%, with a VPP of 100%, and a VPN of 80%. It preceded the clinical symptoms by six days, but it did not precede the CT findings (34). In that same study, the 1,3- $\beta$ -glucan had a sensitivity of 87.9%, a specificity of 43.3%, with a VPP of 40% and a VPN of 96%. This test preceded the clinical symptoms by 4-21 days and the tomographic findings by nine days (34, 35).

Another useful test is a PCR of the fungus DNA, with a sensitivity of 88% and a specificity of 75%. However, one of its drawbacks is that it is a less standardized test (38, 44-47). In the study performed by Hospital de la Misericordia, in the PCR for a cut-off point greater than 40 copies/mk, a sensitivity of 55%, a specificity of 93%, a VPP of 40%, and a VPN of 96% were achieved (34).

Using a CT, an early stage is characterized by nodes with a perilesional frosted glass halo of the pleural base (figure 5). The latter stage contains areas of wedge consolidation (by pulmonary infarct or hemorrhage), cavitation and a sign of increased air flow, which is seen in the convalescence stage, two to three weeks after therapy has started and neutropenia has improved (12,48) (figures 6 and 7).

In two international TACAR studies in the pediatric population, the most frequent findings were nodes or cottony masses, with a percentage of 34.6%, followed by cavitation with 14.4-25%, a halo sign with 6.4% (represents bleeding) a sign of increased air flow of 1.6%, and wedge lesions with 1.1%. Approximately 42% of cases included other infiltrated entities and lesions (5,49,50). On the other hand, in a study performed by Hospital de la Misericordia, the CT findings were the following, in order of frequency: The halo sign, with a percentage of 53%, consolidation with 25%, and the sign of increased air flow with 3%, which are part of the major criteria of the EORTEC/MSG (European Organization for Research and Treatment of Cancer/invasive Fungal Infections Cooperative group and Mucositis Study Group), for the diagnosis of angioinvasive pulmonary aspergillosis.

The halo sign was the most valuable, presenting a sensitivity and specificity of 75%, as well as a VPP and a VPN of 75%. Consolidation had a sensitivity and specificity of 50%, as well as VPP and VPN, and the sign of increased air flow had a sensitivity of 0, with a specificity of 75%, a VPP of 0 and a VPN of 43% (34). The other manifestations which were found by imaging during the study were, frosted glass, with a percentage of 47%, gemmation tree with 13%, nodes with 13%, atelectasias with 13%, pneumothorax with 7%, and a cobble pattern with 7%, which correspond to the minor criteria of EORTEC/MSG (34). These findings differ from international experience findings regarding the pediatric population.

Finally, the aeroinvasive technique, which is frequent in neutropenic and AIDS patients, causes tracheobronchitis, bronchiolitis and bronchopneumonia. The CT shows centrilobular nodes, as well as nodular or linear areas, with the appearance of a gemmation tree (figure 8) (12).

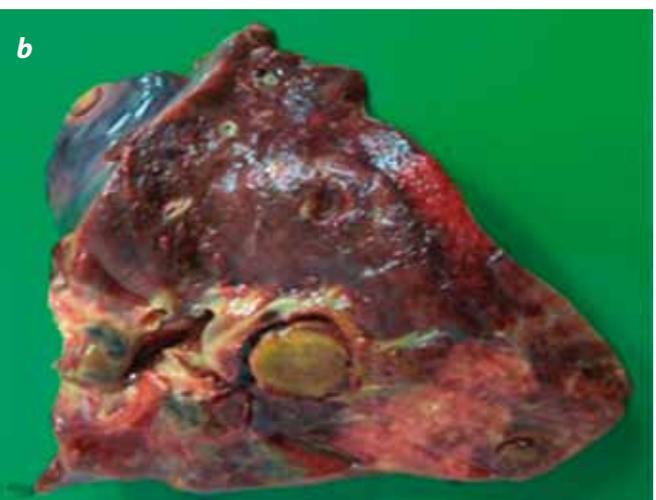
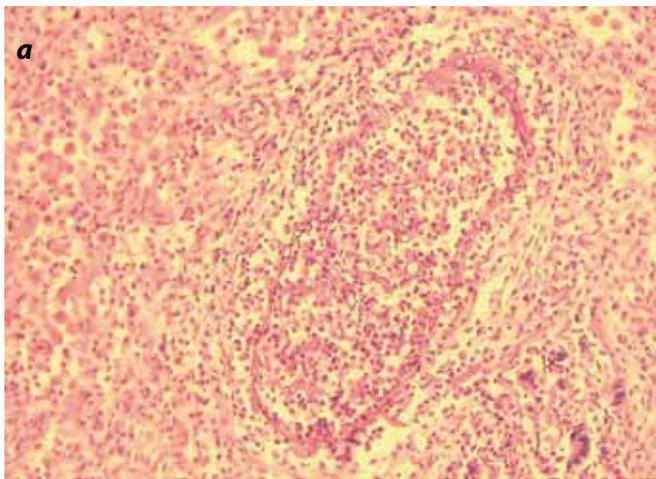


Figure 7. Latter stage of angioinvasive aspergillosis: (a) *Aspergillus* fungi invade the vascular wall, causing thrombi and spreading through the bloodstream (H & E). (b) Invasive pulmonary aspergillosis (acute cavitated): necrotic tissue is separated, forming brown-greenish balls which simulate an aspergilloma.

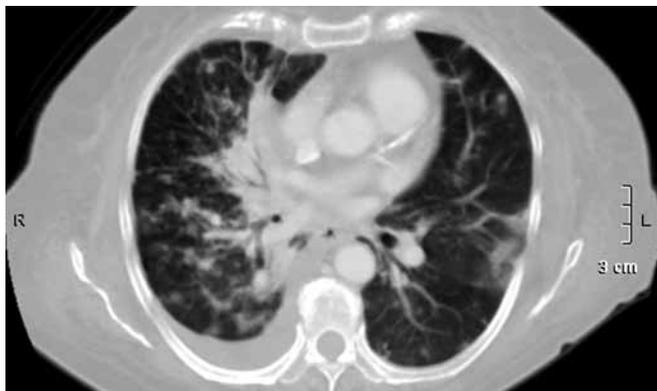


Figure 8. 5-year old patient with history of AIDS, who consults due to a dry cough. The TACAR shows centrilobular nodules in frosted glass in a case of aspergillosis. Pulmonary Aspergillosis by computerized tomography in the pediatric patient.

## Conclusion

The clinical forms of pulmonary aspergillosis vary according to the immunological status of the patient. Among these forms, the invasive forms deserve the most attention given their prognostic importance. Their early diagnosis is based on image and laboratory findings; therefore, the radiologist must be familiarized with the tomographic findings of pulmonary aspergillosis, given that his/her report constitutes a fundamental tool to alert the doctor, so that he/she can establish an early adequate therapy given the implications of the prognosis.

Even though the tomographic findings in Hospital de la Misericordia differ in frequency in respect to international literature, they are part of the major EORTEC/MSG criteria for the diagnosis of invasive pulmonary aspergillosis.

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Received for evaluation: October 30, 2012

Accepted for publication: March 20, 2013