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Science and Art

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Medicine and perhaps neurology, in particular, combines art and science in an exceptional way. Any evaluation of a patient, however, simple what afflicts him is, implies conjunction of activities that will finally lead us to a diagnosis.

The observation of an individual on their arrival to the consultation room or emergency room and listening attentively to the situational approach according to the description of the one who suffers and of those who have witnessed it. The directed interrogation allows the clinician to know the before, the beginning, the evolution, and the current situation and the administered treatments and response to these, the background, and how the systems and organs that have not been affected or have been partially affected are.

Afterward, comes the exhaustive search for signs from head to foot, from cognition, cranial nerves, motricity, sensitivity, cerebellar activity, meningism, and the patient's march; all of this to integrate syndromic, topographic, etiological, final, and differential diagnostics. To make decisions on complementary studies that allow us to demonstrate or deny our diagnostic approaches and to always offer a therapy that in our reach and that of our patient can provide the maximum benefit.

So far, it seems clear that the doctor constantly establishes the application of the scientific method in his practice on a daily basis; he observes, establishes a diagnostic hypothesis, experiments on a therapy based on the semiological conjunction of what was found, and establishes a theory that coincides with the findings in the requested laboratory and image examinations.

To practice medicine appears to be simple work, but it really is not, simply because to know how to evaluate each symptom and sign found, it is necessary to have acquired the epidemiological, anatomical, physiological, genetic, biochemical, molecular, imagnological, hematological, and pharmacological knowledge (among much others).

What we previously treated as a movement disorder called Korea, which together with a pattern of autosomal dominant inheritance and progressive cognitive impairment was then called Huntington's disease, we must now demonstrate to be an alteration in the short arm of chromosome 4 in the huntingtin gene, which will be expressed as an exaggerated number of CAG repetitions (more than 40) in the first exon encoding of the protein called polyglutamine. Today, we speak of diseases of channels (channelopathies), proteins (proteinopathies), enzymes, etc. The doctor's work has become complex and enormously challenging because it is not enough to be assisted by a computer to solve a problem, one must also have the needed educational and cultural background.

As if it was not enough, doctors today must also be artists, capable of interpreting in the patient's voice the anxiety he conveys, of scrutinizing the cry of despair he contains, and who, if clever enough, will be able to alleviate and reassure the one who suffers. It is an art to
be empathetic, to find a way to console, and to reassure the one who is afraid to suffer the untreatable. It is an art to know how to listen patiently to a story that at times is lost and to reorient the conversation without giving the impression of no longer wanting to listen or of feeling annoyed by it. It is an art to look into the eyes with contagious serenity, with the honesty that calms, with the joy that comforts, with the cleanliness that gives confidence. It is an art to know how to embrace without smothering, to touch without bothering, to listen for relieving, to see and discover the hidden, to feel the pain of others, to smell the infectious process, and to speak with the wisdom of the learned but with the humility of one who recognizes all his limitations.

It is our work and especially that of the neurologist to put together science and art, and to observe, listen, feel, and draw from memory all stored information that may be of use; correlating data, establishing possibilities and deciding what to offer seeking the well-being of the other with the least possible risk of harm. It is through this challenging work that day by day we get to experience unrepeatable stories, unparalleled challenges, hopes that seem unreachable and miracles that cannot be explained.

Medicine, and especially neurology, is a wonderful profession that allows many of us to feel like our days are always different that our patient is unique and that our life is really full of meaning.
Experience in the treatment of meningitis associated with health care in pediatric patients

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Abstract

Objective: The objective of the study was to describe our clinical experience in meningitis associated with health care (MAHC).

Methods: A retrospective study included pediatric patients, with MAHC, from 2010 to 2017. Parametric variables were evaluated by media, standard deviation, media and interquartile range. Non-parametric variables were described by reasons and proportions, Chi-square IC 95%. Significant variables (p < 0.005) were evaluated by bivariate logistic regression model to identify related risks for adverse evolution. We obtained the approval of the research ethics committee of our hospital for publication of this data.

Results: A total of 114 cases of MAHC in children were analyzed. There were Gram-negative bacilli (62.6%) and ESBL producers (42.4%). Mortality was higher amongst cases exposed to more than three antibiotics OR = 5.50 (IC 95%, LI 0.996, LS 30.36) sig 0.050 mortality correlation 0.847.

Conclusions: Gram-negative bacteria are frequent in MAHC, mortality was correlated to exposition more than three antibiotics.

Key words: Meningitis. Acinetobacter baumannii. Antibiotics.
Introduction

Meningitis associated with health care (MAHC) or nosocomial origin, usually of bacterial etiology, can be a consequence of invasive procedures: craniotomy (0.8-1.5%) internal ventricular catheters (4-17%) or external (8%), lumbar puncture (x1 every 50,000), intrathecal infusion of medications, spinal anesthesia (0.8-5%), complicated head injury (1.4-25%), or metastatic infection in patients with acquired bacteremia1-3. MAHC episodes can be diagnosed during the hospitalization period and up to one year after its onset. It is often produced by multiresistant bacteria, unlike the bacteria that cause community meningitis4.

In recent years, there has been a reported decrease in the incidence of MAHC, although report of permanent sequelae and frequent association with coagulase-negative Staphylococcus persists; nevertheless, participation of Klebsiella pneumoniae, Pseudomonas aeruginosa, Escherichia coli, and Acinetobacter baumannii are relevant; often multidrug-resistant (MDR), especially related to use of broad-spectrum antibiotics5-9.

The term MDR refers to the expression of bacterial resistance to at least one agent in ≥ 3 antibiotic categories. We define a bacterium as extra drug resistant (XDR), when it is not susceptible to more than one antimicrobial agent in at least two antibiotic categories. Resistant bread (PDR) refers to bacterial expression of resistance to all antibiotic categories; particularly, values of minimum inhibitory concentration (MIC) are more useful than category of sensitive, intermediate, or resistant10.

Mortality related to MAHC ranges from 9% to 33% depending on the causative agent11,12. The objective of this study is to describe our clinical experience in MAHC treatment through the evolution of cases.

Methods

We carried out a retrospective, descriptive study, between 2010-2017. All pediatric patients hospitalized with a diagnosis suggestive of MAHC in the pediatric division of the Civil Hospital of Guadalajara “Fray Antonio Alcalde” were included in a non-randomized sample (for convenience).

Hospital Civil de Guadalajara Fray Antonio Alcalde, a 1000-bed it is a tertiary care teaching hospital. The hospital provides services to the Jalisco state and its capital, Guadalajara, the second-largest city in Western Mexico, as well as to surrounding states. The hospital consists of adult and pediatric beds. All of the pediatric units are located in one building. There are two neonatal intensive care units (ICUs) and one pediatric ICU. In 2018, there were 7398 patients discharged from the pediatric ward; 300 patients were submitted to neurochirugica treatment.

Patients who met the clinical and laboratory criteria issued by the Centers of Disease Control and Prevention (CDC)’s National Healthcare Safety Network of 2017 (NHSN), and the official Mexican Standard of Epidemiology for Disease Prevention and Control NOM-026 SSA2-1998 were included in the study.

We review patients from 1 month to 14 years and 11 months of age who, having undergone some neurosurgical procedure such as placement of Ventricular Peritoneal Shunt Valve (VPSV), drainage of hematoma, biopsy or resection of brain tumor, among other procedures without other evident focus of infection. They developed meningitis data in the following 14 days and up to 1 year after placement of cerebrospinal fluid (CSF) drainage devices, which were also accompanied by MAHC definition.

Definition

According to the Meningitis and Ventriculitis Management Guidelines of 2017 CDC/NHSN associated with health care are defined, as a patient with bacterial growth in CSF culture, or a patient with at least two signs and symptoms of fever > 38°C or hypothermia < 36°C, headache, apnea, bradycardia, irritability cranial or meningeal signs, in addition to abnormal analysis of CSF cytochemistry (hyperproteinorrachy, hypoglycorrhachia, and hypercellularity for central laboratory ranges); organisms seen in Gram-stain, bacteria grown in CSF and blood.

Demographic data, comorbidities, clinical manifestation, as well as microbiological and radiological reports of patients, were recorded together with the antibiotic treatment and its duration. Bacterial isolates in blood and CSF as well as the determination of bacterial antibiotics sensitivity were analyzed by antibiogram performed by VITEK 2 automated method. Durham California, based on the Clinical and Laboratory Standards Institute (CLSI) formerly the National Committee for Clinical Laboratory Standards as well as the final evolution of each case such as: therapeutic failure, cure, death, relapse or reinfection, were evaluated by at least two infectious pediatricians and the information of cases was registered on an Excel database and analyzed by means of Statistical Package for the Social Sciences IBM SPSS 23.0.
Table 1. Demographic characteristics in 114 episodes of nosocomial meningitis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value (%)</th>
<th>Media</th>
<th>Desv. Std.</th>
<th>Inter quartil range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age months</td>
<td>45.7</td>
<td>31.9</td>
<td>37.5</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>49 (43)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>65 (57)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital stay</td>
<td>46</td>
<td>32</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>CVC* time</td>
<td>96 (84.2)</td>
<td>24</td>
<td>21</td>
<td>34</td>
</tr>
<tr>
<td>Previous antibiotics</td>
<td>82 (72)</td>
<td>3</td>
<td>3.1</td>
<td>3</td>
</tr>
<tr>
<td>VPSV** (days postinsertion)</td>
<td>57 (50)</td>
<td>79</td>
<td>156</td>
<td>90</td>
</tr>
<tr>
<td>Ventriculostomy (duration days)</td>
<td>63 (55)</td>
<td>6</td>
<td>8.5</td>
<td>10</td>
</tr>
<tr>
<td>Neurochirurgic procedure</td>
<td>60 (52.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSF fistula†</td>
<td>20 (17.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agents in CSF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram-negative bacteria</td>
<td>59 (51.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram-positive bacteria</td>
<td>33 (29)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candida</td>
<td>4 (3.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymicrobial</td>
<td>7 (6.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>11 (10.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leucocytes ($\times 10^9$)</td>
<td>14.500</td>
<td>6.889</td>
<td>10.610</td>
<td></td>
</tr>
<tr>
<td>Plaquetas ($\times 10^9$)</td>
<td>453.254</td>
<td>155.783</td>
<td>256.700</td>
<td></td>
</tr>
<tr>
<td>CRP‡ (mg/dL)</td>
<td>96.6</td>
<td>102.1</td>
<td>144.6</td>
<td></td>
</tr>
<tr>
<td>PCT§ (mmol)</td>
<td>9.3</td>
<td>27.7</td>
<td>3.32</td>
<td></td>
</tr>
<tr>
<td>CSF glucose (g/L)</td>
<td>29.6</td>
<td>27.5</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>CSF protein (g/L)</td>
<td>8.1</td>
<td>2.4</td>
<td>0.694</td>
<td></td>
</tr>
<tr>
<td>CSF cells</td>
<td>3851</td>
<td>16587</td>
<td>432</td>
<td></td>
</tr>
</tbody>
</table>

*Central venous catheter.  
**Ventricular peritoneal shunt valve.  
†Cerebrospinal fluid.  
‡C‑reactive protein.  
§Procalcitonin.

Ethics

Standard treatment for nosocomial meningitis was administered to all patients. The study was approved for its execution and publication by the research ethics committee of the Civil Hospital of Guadalajara “Fray Antonio Alcalde” with registration number 026/18.

Statistic analysis

Parametric variables were evaluated with means, standard deviation, and interquartile range. Non-parametric variables were described by means of ratios, proportions, compared with Chi-square 95% CI. All significant variables (p < 0.05) were subjected to a bivariate logistic regression model, to identify risk factors related to adverse evolution.

Results

Demographics

Between 2010 and 2017, we collected clinical data from 118 episodes of MAHC from 86 patients. We exclude four cases due to insufficient data.

Included patient’s ages were from 1 to 200 months of age in their majority; they were carriers of meningitis associated with VPSV (44/51.7%).

Once the MAHC diagnosis was made, the shunt device was removed within the next 24-72 hours; in each case the patients were subsequently subjected to the placement of an external CSF device.

Change of ventriculostomy was carried out every 7-10 days, until obtaining bacterial negativization, with subsequent resolution of infectious process.
replacement of a new CSF derivation system, when it was necessary.

Two-thirds of patients received antibiotics before admission for their treatment, on average three antibiotics; 80% of children required antibiotics infusion through central venous catheter, 23 days on average (Table 1).

**Treatment and evolution**

We started an antibiotic scheme guided by a Gram stain of CSF. According to our epidemiology, included for treatment vancomycin and cefepime prescribed at weight and meningeal doses.

In case not having growth in the first CSF culture, treatment was directed based on Gram-stain findings and subsequent CSF cultures, taking into account in addition, results of blood cultures for its final classification as Gram-positive bacterial meningitis, Gram-negative bacterial meningitis, mixed bacterial meningitis or by Candida species.

Single or polymicrobial etiology, and consistent on bacterial or yeast growth were obtained from a first CSF culture on 89.5% of the samples.

Bacteremia associated with meningitis was isolated in 28/100 cases, but only 7% (8/28) of those were related to the same causative agent. Bacteremia of a different etiology associated with catheter was considered as a coinfection with meningitis.

We obtained an isolation of 71 Gram-negative strains (62.6%). Derived from antibiotic resistance phenotype producing extended-spectrum beta-lactamases (ESBL) in Gram-negative bacteria, these strains received meropenem alone or in combination with rifampicin. Two strains of *Elizabethkingia meningoseptica* were resistant to vancomycin and treated with trimethoprim/sulfamethoxazole.

The most common Gram-negative agent in meningitis cases was *A. baumannii* 30 (42.25%), all of these cases were considered as a therapeutic failure secondary to meropenem resistance.

In addition, 15 cases (21.1%) of Gram-negative bacterial infection, among them: *P. aeruginosa, K. pneumoniae,* and *E. coli*; they did not show clearing of CSF in more than 10 days of treatment also with clinical symptoms, they were considered with therapeutic failure to cefepime and meropenem, even though the antibiogram showed sensitivity to meropenem.

All these cases received colistimethate intravenously at a dose of 10 mg/kg (125,000 IU), and intrathecal at a dose of 10 mg/kg of impregnation followed by 5 mg/kg (75,000 IU) per day, in addition to oral rifampicin, until CSF clearing.

Among the Gram-positive bacteria, a strain of *Enterococcus faecium* was resistant to vancomycin and linezolid; it received 4 weeks of treatment with daptomycin. Finally, four cases with meningitis due to methicillin-sensitive *Staphylococcus aureus* (MSSA) were treated with vancomycin/rifampicin combination, for 20 days, on average 16 days and sensitivity to vancomycin with a MIC < 1 μg/mL, all cases were coinfectcd.

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**Table 2. Evolution of 114 cases of MACS according to the type of agents isolated in CSF**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Healing</th>
<th>Reinfection</th>
<th>Death</th>
<th>Death OR</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>IC 95%</td>
<td></td>
</tr>
<tr>
<td>CNS</td>
<td>11 (50)</td>
<td>6 (27.3)</td>
<td>3 (13.6)</td>
<td>0.78</td>
<td>22 (19.3)</td>
</tr>
<tr>
<td>MSSA</td>
<td>0</td>
<td>1 (25)</td>
<td>3 (75)</td>
<td>5.1</td>
<td>4 (3.5)</td>
</tr>
<tr>
<td>MRSA</td>
<td>2 (50)</td>
<td>2 (50)</td>
<td>0</td>
<td>0.52</td>
<td>4 (3.5)</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>7 (63.6)</td>
<td>2 (18.2)</td>
<td>1 (9)</td>
<td>0.08-3.46</td>
<td>11 (9.7)</td>
</tr>
<tr>
<td>Candida</td>
<td>4 (66.6)</td>
<td>1 (18.6)</td>
<td>1 (16.6)</td>
<td>1</td>
<td>6 (5.2)</td>
</tr>
<tr>
<td>GNB MR</td>
<td>16 (50)</td>
<td>11 (34.4)</td>
<td>6 (18.8)</td>
<td>1.18</td>
<td>32 (28)</td>
</tr>
<tr>
<td>GNB ESBL</td>
<td>13 (46.4)</td>
<td>10 (35.7)</td>
<td>3 (10.7)</td>
<td>0.57</td>
<td>28 (24.6)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (28.6)</td>
<td>3 (42.9)</td>
<td>2 (28.6)</td>
<td>6.29</td>
<td>7 (6.1)</td>
</tr>
</tbody>
</table>

|                      | 48 (42.1) | 36 (31.6) | 19 (16.6) | 114 (100) |

CNS: central nervous system; MSSA: *Staphylococcus aureus* sensitive methicillin; MRSA: methicillin-resistant *Staphylococcus aureus*; GNB MR: gram-negative bacterial meropenem resistant; GNB ESBL: gram-negative bacteria extended-spectrum beta-lactamase producer.
by Gram-negative nosocomial agents producing ESBL or by fungemia.

Distribution of cure rate, death, and reinfection outcome between different bacterial and fungal etiologies was similar, no differences were found by means of Chi-square analysis (Table 2).

Complications

In 51 episodes (44.7%), we recorded at least one nosocomial acquisition coinfection, there was predominance of catheter-associated bacteremia (28/24.6%), two of them complicated with endocarditis, and two with fungemia.

Other complications included: intra-cerebral abscesses or septate ventriculitis 29 (25.4%), azote elevation 11 (10%), and transaminiasemia 15 (22.1%). These complications were prevalent among Gram-positive meningitis group; they were treated with vancomycin, which returned at normal levels after the end of antibiotic treatment.

After MAHC diagnosis, we found neurological sequelae in 68 (83.5%), all of them were patients in whom hemorrhages or intra-cerebral infarctions were associated, epilepsy of recent onset and cognitive deterioration, blindness or deafness. The evolution of cases is shown in table 2.

Microbiological characteristics of isolated agents

We were able to identify on the first CSF sample of the 114 episodes of meningitis: four species of Candida (3.5%), none of them resistant to azoles, and amphotericin B or caspofungin 59 (51.7%).

The most frequent bacterial isolates in CSF were Gram-negative ESBL-producing phenotype 25 (42.4%). Enterobacter cloacae, Escherichia coli and Pseudomonas aeruginosa were the most prevalent strains. Thirty one (52.5%) bacterial strains with carbapenemase-producing phenotype, K. pneumoniae, P. aeruginosa, Enterobacter cloacae, and A. baumannii, they had 39% share (23) of these isolates, a MIC for colistimethate minimum 1 and maximum 16 μg/ml, two strains were XDR, and the rest MDR.

As of 2010, resistance to meropenem of Gram-negative bacteria was determined through the resistance to antibiotics of all classes, by means of the antibiogram and relation with the lack of CSF bacterial clearance, in addition to persistent symptomatology of MAHC, in all cases of etiology by A. baumannii.

Among Gram-negative bacterial isolates, resistance to carbapenems was frequently the second phenotype found among strains of K. pneumoniae, P. aeruginosa, Enterobacter cloacae, and A. baumannii, responsible for 30 (81%) of cases in this group, with MIC for colistimethate minimum 1 and maximum 16 μg/ml, two strains were XDR and the rest MDR.

We identified 37 (32.5%) Gram-positive bacteria and in 9 samples of CSF (7.9%) growth with two simultaneous agents that included ABMDR or ESBL-producing Gram-negative bacteria and Candida species sensitive to amphotericin B. Eleven (9.6%) cultures were reported as negative, although in Gram stain bacteria were seen, probably due to antibiotics use before diagnosis (Fig. 1).
A second culture on all CSF was practiced between the 3rd and 5th day; they were reported without growth in 56% of primary isolates (Fig. 2). Antibiotic resistance phenotype of strains isolated in first CSF is shown in figure 3.

**Risk factors for severity and mortality**

The cumulative mortality rate was ×16.66/100 cases. Higher mortality frequencies were observed among male patients 57.8%, those patients who developed MACS after a neurosurgical procedure 68%, in children carriers of some nosocomial infection added as endocarditis 68.4%; finally, 42% of mortality was observed among episodes of meningitis due to Gram-negative bacteria, half of them were secondary to *A. baumannii* MDR.

Notoriously, although 75% of patients with MSSA meningitis associated died; mortality in general by this factor corresponded to 17.6%.

However, only exposure to more than three antibiotics resulted in binary logarithmic regression with the method of successive backward conditional steps with OR = 5.50 (95% CI 0.996 LS 30.36) sig 0.050 death correlation −847.

**Discussion**

MAHC follow-up studies recorded frequencies of 6%, especially in young children, commonly associated with prolonged permanence of external CSF drainage systems, tumor etiology in children with VPSV mortality of 22%12.

As of 2005, it has been reported that coagulase-negative *Staphylococcus* and *S. aureus* are associated with VPSV up to 65%, with an increase in the participation of MRSA in people with chronic processes such as hydrocephalus and in young children. The nosocomial acquisition is usually less severe than that acquired in community that was associated with a hematogenous origin15.

To achieve therapeutic levels before surgery, our patients received in 95% of the time, at least 24 h of cephalothin prophylaxis for CSF external bypass and for VPSV, latter were of regular type without antibiotic impregnation.

In our study, the average time to develop meningitis associated with VPSV placement was 8 days after device placement, as reported in other studies9.

Special attention is required for cases of MSSA infection that had a 75% mortality rate in spite of vancomycin treatment, some publications have theorized that participation of P Valentin protein in strains of community origin may be of poor prognosis, but in our study lack of molecular biology tool, could had predicted greater severity and mortality was a vulnerability12,14.

Against the odds was expected, the predominance of isolated bacteria was mostly Gram-negative with ESBL-producing antibiotic resistance phenotype and *A. baumannii* MDR.

In one-third of these children, it was necessary to use intravenous and intrathecal colistimethate, which also was not free of resistance in 7% of the isolates of *A. baumannii*, one of *P. aeruginosa*.

In our hospital, the first case of *Acinetobacter baumannii* carbapenems resistant was detected in 1999, since then we have observed the dissemination of this agent in all areas of hospitalization for adult and pediatric patients. During 2011 frequency of participation in processes associated with health care, for neurosurgical area corresponded a frequency of 5.6% and in pediatric area 1%15.

A finding of importance was the isolation of three strains of *E. meningoseptica*, which has been reported in neonatal sepsis outbreaks and is considered to be a Gram-negative agent sensitive to vancomycin16.

Mortality in our study for *A. baumannii* corresponded to 21%, while in other publications, it corresponded between 10% and 71% even with use of colistimethate as a salvage treatment17,18.

Although 11 cases had no growth of bacteria in CSF, we decided to analyze them, because we found bacteria present in Gram stains reviewed by at least two infectious pediatrician. This parameter has been shown to be useful in up to half of the cases of meningitis in which cultures had no bacterial growth but with chemical findings suggestive19.
We suggest that the lack of growth of bacteria in blood and CSF was probably secondary to the previous use of antibiotics, on average three except among episodes of Candida etiology that received seven antibiotics as a mean for infectious processes of nosocomial bacterial origin.

Limitations and biases of this study are based on the availability for determination of lactate, procalcitonin, and C-reactive protein in CSF, by our laboratory. Not all bacterial strains could be subjected to a regular determination of sensitivity to bacterial agents, especially colistimethate.

With the exception of colistimethate, all antibiotics used were of generic origin, at appropriate doses, and in duration. We also do not have molecular tools for microbiological diagnosis to determine specifically types of resistance.

In addition, the inability to analyze biofilms in shunts and venous catheters prevents knowing the type of biofilm and the extent of antibiotic therapy as well as the possibility of permanence right there. Moreover, finally, in limitation of hospital resources such as availability of operating rooms, surgical shifts, and access by relatives of patients to pay for VPSV antibiotics impregnated and external drainage systems of CSF.

Conclusions

It was remarkable the participation of *A. baumannii* MDR, especially in cases where the patient was exposed to broad-spectrum antibiotics, for these cases, although colistimethate can be a salvage treatment, it is an option that already shows resistance and has been transferred to other Gram-negative bacteria.

In our population, the etiology of MAHC by Gram-positive bacteria was associated with a higher mortality risk, associated with other nosocomial infections.

To reduce bacterial resistance, in the future, we must adhere to recommendations of management guidelines for meningitis, in particular, shorten the time of exposure to external drains of CSF and use VPSV impregnated with antibiotics to limit re-infection.

It is essential to always count in hospital units with molecular tools to identify antibiotic resistance.

Acknowledgment

This research project was carried out without support from external financiers. We declare that there is no conflict of interest. The work group would like to thank the Microbiology Laboratory staff at the Civil Hospital of Guadalajara “Fray Antonio Alcalde”, for their invaluable help.
Neurocysticercosis in cancer patients

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Abstract

Introduction: Neurocysticercosis (NC) is considered as a public health problem. Meanwhile, cancer is the second cause of death around the world. The coexistence of both conditions had been scantily reported or studied. Objective: The objective of the study was to investigate and report the presentation of NC in patients with systemic cancer. Methods: Patients with confirmed cancer and NC at a referral center from January 2012 to June 2017 were included. Demographic, clinical, and radiologic findings were presented. Results: Eighteen cancer patients were diagnosed with NC. Within a mean follow-up period of 45.2 months, one died from complications directly related to NC, and seven had associated cancer progression. Headache and seizures were the most common symptoms that led to the diagnosis of NC. The number of lesions seen ranged from 1 to 100. Conclusions: The estimated incidence of NC and cancer is not low and should be considered a differential diagnosis of brain metastases, especially in developing countries.

Key words: Neurocysticercosis. Cancer. Epidemiology. Developing countries.
Introduction

Neurocysticercosis (NC) is caused by the larvae or cysticerci of *Taenia solium*. One of the most striking features of NC is its heterogeneous clinical picture, which can range from asymptomatic to severe life-threatening neurologic syndromes. The disease severity and clinical manifestations are indicative of infective burden, location, and the host’s immune response. In many developing countries, such as in our country, NC is a frequent medical condition, with reported frequencies as high as 9.1%. The diagnosis of NC is made by neuroimaging techniques with either computer tomography (CT) or magnetic resonance imaging (MRI). Meanwhile, the lifetime probability of having invasive cancer is 39.7% for men and 37.6% for women. With an annual death rate of 168.3 per 100,000 population and an approximate cancer incidence of 418-502/100,000 population, cancer is one of the most common causes of mortality and morbidity.

Information concerning NC and cancer is hardly found in medical literature. Some have suggested that the elicited chronic inflammatory reaction, evasive mechanisms, and molecular mimicry capacity of *T. solium* induce immunosuppression, which can be associated with cerebral gliomas and hematologic malignancies. A postmortem study reported that 21% of patients with NC had a malignancy, and some have proposed the pathogenic mechanisms. The purpose of this study was to report the presentation of NC in patients with systemic cancer.

Methods

A database that was prospectively acquired from January 2012 to June 2017 was analyzed. All patients seen by the neuro-oncologic clinic of a referral cancer center (Instituto Nacional de Cancerología, Mexico City) were included. The demographic information, oncologic history, signs and symptoms, treatment, and median overall survival rates were collected. All patients had histopathologic confirmation of their primary cancer. The diagnosis of NC was made by a combination of clinical features and MRI. Active infection was diagnosed with the presence of active cysts in the vesicular, colloidal vesicular, and/or granular nodular stages on MRI. Overall survival was measured from the time of the first neuro-oncologic consultation until death or the last reported visit. The Institutional Ethics and Scientific Investigation Committees approved data acquisition and analysis.

Table 1. General characteristics of patients with NC

<table>
<thead>
<tr>
<th>Patients characteristics</th>
<th>n = 18 (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>13 (72.2)</td>
</tr>
<tr>
<td>Male</td>
<td>5 (27.7)</td>
</tr>
<tr>
<td>Primary site of cancer and stage</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td></td>
</tr>
<tr>
<td>I (1)</td>
<td>5 (27.7)</td>
</tr>
<tr>
<td>II (2)</td>
<td></td>
</tr>
<tr>
<td>III (2)</td>
<td></td>
</tr>
<tr>
<td>Ovarian</td>
<td>3 (16.6)</td>
</tr>
<tr>
<td>NE (2)</td>
<td></td>
</tr>
<tr>
<td>IV (1)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>III (1)</td>
<td></td>
</tr>
<tr>
<td>IV (1)</td>
<td></td>
</tr>
<tr>
<td>Urologic</td>
<td>3 (16.6)</td>
</tr>
<tr>
<td>NE (1)</td>
<td></td>
</tr>
<tr>
<td>IV (2)</td>
<td></td>
</tr>
<tr>
<td>Skin/Melanoma</td>
<td>3 (16.6)</td>
</tr>
<tr>
<td>NE (1)</td>
<td></td>
</tr>
<tr>
<td>II (1)</td>
<td></td>
</tr>
<tr>
<td>III (1)</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>1 (5.5)</td>
</tr>
<tr>
<td>IV (1)</td>
<td></td>
</tr>
<tr>
<td>Head and Neck</td>
<td>1 (5.5)</td>
</tr>
<tr>
<td>IV (1)</td>
<td></td>
</tr>
<tr>
<td>Systemic metastases other than the CNS</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>4 (22.2)</td>
</tr>
<tr>
<td>Absent</td>
<td>14 (77.8)</td>
</tr>
<tr>
<td>Any clinical manifestation</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>10 (55.5)</td>
</tr>
<tr>
<td>Seizures</td>
<td>6 (33.3)</td>
</tr>
<tr>
<td>Intracranial hypertension</td>
<td>4 (22.2)</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>3 (16.6)</td>
</tr>
<tr>
<td>Ataxia</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>Decreased awareness</td>
<td>1 (5.5)</td>
</tr>
<tr>
<td>None</td>
<td>8 (44.4)</td>
</tr>
<tr>
<td>Diagnosis of NC</td>
<td></td>
</tr>
<tr>
<td>Before the diagnosis of cancer (100-140 months)</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>After the diagnosis of cancer (2-191 months)</td>
<td>16 (88.8)</td>
</tr>
</tbody>
</table>

NE: Non-specified

Results

The general characteristics are presented in Table 1. Of the 18 patients included in this study, 13 (72%) were women. The mean age was 61 ± 15 years (range, 36-85 years) at the time of cancer diagnosis and 58 ± 15 years (range, 25-84 years) at the time of NC diagnosis. During the study period, no patient developed...
Central Nervous System (CNS) metastases, and four patients developed metastases to sites other than the CNS (i.e., mediastinum, bone, lung, and suprarenal gland). The number of lesions seen on MRI was one or two in most patients (n = 13) and ≥3 in 5 patients, of which one patient presented with >100 lesions.

The characteristics of the NC lesions are presented in table 2. Three patients showed signs of intracranial hypertension; two of them were treated with decompression surgery and, if considered by the neurosurgical team, excision of the intraventricular cysts, and one of them required three surgical interventions. During a mean follow-up period of 45.2 months (range, 1-147 months), eight deaths were reported. One patient who had a previous history of multiple NC reactivations developed NC recurrence and refractory status epilepticus; he died a month after the diagnosis. The other seven deaths were directly related to cancer progression. The median overall survival was 45 months (95% CI 21.7-68.6). Figure 1 illustrates the NCC findings on MRI. All patients with active infection received steroids, followed by albendazole at 15 mg/kg per day.

**Table 2. Characteristics of NC lesions**

<table>
<thead>
<tr>
<th>NC stage</th>
<th>No. of patients (%)</th>
<th>NC location (No.)</th>
<th>No. of lesions &gt; 3 (5)</th>
<th>&lt;3 (13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vesicular</td>
<td>9 (50%)</td>
<td>ES 3</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EI 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>I 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcified nodular</td>
<td>6 (33.3%)</td>
<td>ES 2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EI 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>I 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple (&gt;2 stages)</td>
<td>3 (16.6%)</td>
<td>ES 1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Both (E-I) 2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ES: extraparenchymal subarachnoid; EI: extraparenchymal intraventricular; I: intraparenchymal; E: extraparenchymal. No patient had granular nodular, colloidal vesicular, or non-cystic phases; NC: neurocysticercosis.

**Discussion**

*T. solium* cysticercosis is a globally reemerging disease, with an increasing number of cases in previously considered non-endemic countries, such as the USA, Canada, Australia, Japan, and Europe. We presented 18 patients with NC who concurrently had systemic cancer; majority comprised women and had a mean age that was similar to that previously reported by others. The most common symptoms that led to the diagnosis were headache and seizures. During follow-up, one of the patients died from NC-related complications, and seven died because of cancer progression. All patients were initially considered as having CNS metastases; MRI, other advanced techniques, such as positron emission tomography–computed tomography (PET/CT), and response to steroids/antiparasitic treatment helped in distinguishing NC from CNS metastases. MRI showed multiple NC lesions, and the most common finding was the vesicular stage.

Tapeworm infections have accompanied humans for more than 100,000 years. Characterization of the genomes of these parasites, as well as a deeper understanding...
of their molecular markers and the host–parasite relationship\textsuperscript{10}, has improved diagnosis, treatment, and prevention. The diagnosis of NC is made by neuroimaging techniques, such as CT or MRI. The characteristics of NC vary according to the phases of development, including non-cystic, vesicular, colloidal vesicular, granular nodular, calcified nodular vesicular, and colloid to calcified stages. One of the known features of NC is the presence of multiple phases in the same patient\textsuperscript{11}. Some have proposed a serological test to confirm the diagnosis. The most recommended study is the enzyme-linked immunotransfer blot because of its high specificity and sensitivity in the context of active lesions. It uses purified glycoprotein antigens from \textit{T. solium} in either cerebrospinal fluid (CSF) or serum samples. Enzyme-linked immunosorbent assays are better for CSF than for serum samples, but these are not fully recommended because of the poor specificity and sensitivity\textsuperscript{12}. These serologic diagnostic studies are not used frequently and are not currently required for the diagnosis of NC\textsuperscript{13,14}.

Some limitations should be considered in the present study. There may have been selection bias because it was done at a single cancer referral center, the studied population was high-risk, and only patients who were referred for neuro-oncologic consultation were included. To avoid information bias, all data had strict definitions, and all information was evaluated by the main author (BC). This study was not a population-based report and did not aim to review all of the MRI studies done at the institution to establish frequency.

Conclusion

In conclusion, although some have postulated that NC increases the risk of glioma and stroke, we consider that the relationship between NC and the development of CNS metastases is worth exploring, as the others have proposed\textsuperscript{15}. In this study, none of the patients with NC developed simultaneous or asynchronous CNS metastasis. Perhaps, the excessive TH2 response seen in NC\textsuperscript{16} is responsible for that effect, in some extent. A series of certain HLA haplotypes, which have been considered to affect the susceptibility to NC infection\textsuperscript{17,18}, will now be studied further at our institution. The estimated incidence of NC and cancer is not low and should be considered a differential diagnosis of brain metastases, especially in developing countries.

Conflict of interests

None to declare.

Funding

None to declare.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

References

Pilot study: Neuropsychological association of orbitomedial and dorsolateral executive functions in children with behavioral problems

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Abstract

Objective: This proposal addresses the neuropsychological characterization of dorsolateral and orbitomedial executive functions in children with behavioral problems, to identify the functioning level of the cognitive skills associated with this brain area. Materials and methods: The Latin American version of Swanson, Nolan, and Pelham IV scale was applied for the cutoff point of the behavioral difficulties and the Neuropsychological Assessment Battery of Executive Functions (II) with orbitomedial and dorsolateral scales. Sample: The sample was 71 in-school students (43 girls and 28 boys between ages 8 and 14). Results: There is evidence of association of the group under analysis with difficulties in orbitomedial executive skills (in Stroop A [time], and Stroop B [time]) and dorsolateral executive skills (in Semantic Classification [time]). Conclusions: The fullness and efficacy of executive functions dependent on the dorsolateral cortex will depend on the maturity and development of the orbitomedial cortex.

Key words: Prefrontal cortex. Executive functions. Behavior.

Estudio piloto: Asociación neuropsicológica de funciones ejecutivas de tipo orbitomedial y dorsolateral en niños con problemas de comportamiento

Resumen

Objetivo: Esta propuesta aborda la caracterización neuropsicológica de funciones ejecutivas de tipo dorsolateral y orbitomedial en niños con problemas de comportamiento, para identificar el nivel de funcionamiento de las habilidades cognitivas asociadas con estas áreas del cerebro. Materiales y métodos: Se aplicó la versión latinoamericana de las escalas Swanson, Nolan y Pelham IV, para evaluar las dificultades de comportamiento y la batería de funciones ejecutivas de evaluación neuropsicológica (II) para examinar las áreas orbitomedial y dorsolateral. Muestra: La muestra fue de 71 estudiantes escolares (43 niñas y 28 niños de entre 8 y 14 años). Resultados: Se evidenció la asociación del grupo analizado con dificultades en las habilidades ejecutivas orbitomediales (en Stroop A [tiempo] y Stroop B [tiempo]) y habilidades ejecutivas dorsolaterales (en clasificación semántica [tiempo]). Conclusiones: La plenitud y la eficacia de las funciones ejecutivas que dependen de la corteza dorsolateral dependerá de la madurez y el desarrollo de la corteza orbitomedial.

Palabras clave: Corteza prefrontal. Funciones ejecutivas. Comportamiento.
Introduction

The evolution of the prefrontal cortex (PFC) and the development of the frontal lobe show common variations between old world monkeys, apes, and human beings. Different experimental models have shown in the case of the Rhesus monkeys who can learn detailed expectations of the reward, and in their negative favor they reproduce an emotional behavior of frustration\(^1\). This allows to observe that primates and the improvement of the frontal lobe in the control and coordination of cognitive and behavioral processes, manage to organize the behavior according to the environment and the expectations learned, which admit reaching contingencies and, therefore, the organism’s adaptation, which has been related to the negative evaluation of the experiences by the amygdala, and the emotional expression or control of it by the orbitofrontal cortex (OFC) and the medial OFC\(^2,3\).

Certainly, environmental experiences endow the organism with behavioral patterns necessary to respond to contextual demands; a stress response will be mediated by the cerebral amygdala. However, the neurovegetative substrate that allows a hormonal adaptation according to the stimuli will be mediated by the hypothalamus\(^3,4\); obeying that the amygdala is a structure that allows the association of different stimuli, reward, and punishment functions. However, thalamic and amygdala afferents, which are shorter and are activated in the first order, send information to the cortex through the thalamocortical connections to provide the organism with more complex meaning; this way, the unification of these sensory and emotional systems, sent to the cortex through the thalamus, allows this continuous feedback to dissociate emotional functions from the exterior and generate patterns of behavior adjusted to the context\(^3,4\).

According to the aforementioned, the predominant factor or the fundamental role given to the OFC in emotional control and the dorsolateral cortex in the complex planning of behavior toward the environment is evident. It is well known that the efferent pathways of the cerebral cortex toward the thalamus are wider than the afferent ones, because the complex response of behavior will be the specific organized response of the PFC in accordance with the organism’s adaptation to environmental contingencies\(^4\); this way, the medial dorsal nucleus (or dorsomedial nucleus of thalamus) generates projections toward the PFC and provides it with complex functional variables; considering, at a morphological level, that this area of association has a greater number of dendritic spines, which leads to a high functional metabolism\(^5\).

The PFC receives considerable afferents from the thalamus, hypothalamus, limbic system, and different areas of the cerebral cortex, this is how the evolution of this structure in humans has specialized to processes associated with working memory, executive functions, decision-making, the complex function in behavior planning, and discrimination of emotional signals/signaling\(^6\).

The evolutionary process of the PFC is also well known in other species, such is the case of the albino rat whose medial dorsal nucleus (or dorsomedial nucleus of thalamus) generates projections toward the medial PFC, involving different functions along with other basal projections such as motor, olfactory, and autonomic visceral patterns, among others. In line with the aforementioned, the different afferent innervations of the PFC (both thalamic and from different regions of the brain) allow neural activation by AMPA receptors or monoamine receptors from the mesencephalic region, generating cortical excitation; this way, dopaminergic innervation in the PFC of primates has been widely studied, as well as its reciprocation with GABAergic neurons that project to the nucleus accumbens (NAc or NAcc), mediating, and in turn inhibitory regulatory functions\(^6\).

The PFC has serotonergic innervations that come from the raphe nuclei, which apparently helps to mediate the interaction of other neurotransmitters such as catecholamines. Clearly, prefrontal or analogous structures are recognized in primates: to a certain degree Goldberg (2001) – picking up on Brodmann’s findings – describes that apes such as chimpanzees would have 17%, the gibbon and the macaque (the monkey of the old world) 8.5%, and the lemur 7%. Nevertheless, the percentage in humans rises to 29%, which recognizes a greater development in structure and in adaptive processes in comparison to other species. It is also known that this association cortex matures later which is absolutely related to the delay of control of associated behaviors, such as elaborated language in context and reasoning\(^7\).

Several models have been proposed to describe the different components that make up executive functions, sometimes referring to them as an integrated set and at other times as different connectionist structures that allow the development of executive processes with a defined hierarchical structure (such as attentional flexibility, inhibitory control, and working memory)\(^7\). Thus, it can be determined that the functions of attention
receive vital importance since selective attention modulates the flow of information as well as its processing, which in turn allows the consolidation of implicit memory. The theories on the importance of the PFC – already mentioned by Luria posit that dysfunctions in behavior management (e.g., planning, among others), derive from the channeling of such attentional flow as the basis of executive processes; however, comparative studies show differences in their findings suggesting that, possibly, the alternation of different regions is not hierarchized and that, from another perspective, an intertwined collaboration in the present task generates emerging behaviors.

Researches show that executive processes respond to coordinated variables of different regions of the PFC that is modulated in accordance with demanding adaptive processes in the environment. The diversity and heterogeneity of the results reveal functions that may have a hierarchical predominance, but this is not the rule, it seems it is an intermodal function closely related by specific connections that evolved due to adaptive needs. Thus, it can be reductionist to assume that the attentional system can be the regulator of the present information flow, in the sense that it is possible for memory to determine which stimuli to target.

Hence, attention presents a complex arrangement consistent with its close relationship with cognitive flexibility, already referred to by Miyake as a component of alternation that needs several systems which, together, allow access to more complex processes; among these are some systems such as: complex neural systems, multimodal, selective filter, hierarchical system, dynamic system, and supervision of mental activity. Clearly, because of this, the infinity of the intertwined subsystems also links other variables that are important to bear in mind when talking about attention, since it is not only a process that begins with awakening or focusing attention but also involves other processes such as orientation, motivation, processing speed or speed of thought, level of consciousness or concentration, among others.

Finally, attention, as a tracking mechanism of different environmental events presents fundamental bases in the brain stem by means of the ascending reticular activating system. These projections must reach the frontal association cortex, with the right hemisphere as the largest exponent; this way, the involuntary attentional processes will be characteristic of structures related to the diencephalon and mesencephalon, and the more complex processes that require voluntary attention will be related to cortical association structures. This reflects chemical actions to the prefrontal lobes that allow the maintenance of executive actions, which means that an optimal state of attention will be closely related to other basic processes such as memory. Clearly, injuries or affectations in these areas can generate behaviors contrary to those expected by the PFC, such as perseveration and impulsive actions, difficulty in planning, and inadequate organization of behavior, among others.

Following attention, it is important to focus on those contributing processes in the global integrative of executive functions supported by the PFC. The relevance of the substantive actions of social adaptation also depends on the coordination of language, verbal fluency, the way the different verbal constructs are coordinated according to a behavior in a specific context, being able to differentiate semantic content, the relevance of such content in what one wishes to verbalize, the quantity of morphemes, the graphemes used, are all characteristic of a coordinated action of the dorsolateral cortex and OFC. However, it is important to bear in mind that this depends on the access to constructs structured and developed by long-term memory.

In accordance with the above, it is important to deepen in basic aspects to understand the synergy related to executive functions and those processes that the PFC materializes, since the PFC is the fundamental structure to process information and to generate: cognitive flexibility, control in interference, and observation of how memory provides all the significant information in complex tasks.

**Executive processes and the compromise the dorsolateral cortex and OFC**

Different measurement methods in neurosciences allow to demonstrate affectations in different areas of the PFC. According to the evaluation, different compromises can be determined in variables such as cognitive flexibility, attention, and memory. Magnetic resonance imaging (MRIs), computerized axial tomography scan, new technical trends in neuroimaging with a high temporal resolution like the magnetoencephalography, and the new applications created for MRI, have allowed to find functional relationships between trauma and control groups.

Such traumatic processes alter the normal development of information processing, cognitive flexibility, and the mastery/domain of interference to different and repetitive stimuli in the environment. After a traumatic brain injury low-level processes such as the speed of information processing are affected, manifested in difficulty to focus attention on different environmental stimuli, reducing not only visual tracking processes but
also the ability to process information and to voluntarily plan answers or possible behaviors in context\textsuperscript{14}; it is important to point out that the aforementioned lesions keep correspondence (in an integrated manner) with acquired deficits in cognitive flexibility. The evaluation of these processes relies on the capacity (high-level processes) to regulate interference not only environmental but also proprioceptive, possible emotional information coming from the anterior cingulate cortex, and on the ability to use working memory\textsuperscript{9}.

In terms of the acuity of the PFC, there are also features that show the delicate nature of its structures. The abundant connections that innervate the prefrontal area are substantially connected to different subcortical connections; consequently, many explanations are sought to define different pathologies, such as schizophrenia, as mesencephalic lesions during the neurodevelopmental stage, which result in a low mesocortical dopaminergic innervation. This would explain the hypofunction of the cortex and, therefore, the failure in executive control of the striatum (corpus striatum), giving place to the positive symptoms of schizophrenia\textsuperscript{9}.

Certainly, such hypofunction would regulate other chemical processes, such as glutamatergic and GABAergic ones, which help mediate the metabolic activation in the prefrontal lobes. Low activation of the D1 receptors (excitatory dopamine receptor) innervated from the mesencephalic ventral tegmental area would lead to low activity of the dorsolateral PFC (DLPFC or DL-PFC) which, in turn, results in working memory difficulties – observing hypofunctionality in the DLPFC of people with schizophrenia when developing complex tasks\textsuperscript{15}.

The PFC, in its delicate structure, has a wide innervation of granular neurons that have a greater representation of connection routes with the medial dorsal nucleus (dorsomedial nucleus of thalamus). Llinás (2002) promotes the vision of this strong interconnection as the one responsible for the determination of consciousness (“the self”) and the modification of fixed action patterns; such component, confers important variables such as the control of external stimuli functions\textsuperscript{16}. It is also possible to recognize other variables that present alterations during neurodevelopment, some of them characterized by glutamatergic firings in non-NMDA receptors that generate extracellular toxicity and damage of dendritic spines (Díaz and Tirapu, 2017). This added to the synaptic pruning during adolescence – which may be precipitated – and to the difficulties regarding the reorganization of the blood flow\textsuperscript{17}.

In this picture, the PFC has striatal and thalamic connections that generate a feedback loop between the globus pallidus, the ventral anterior nucleus, and the ventral lateral nucleus of the thalamus and the caudate nucleus, to which Goldberg (2001) confers importance for its role in the control of movement and characterizes as part of the frontal lobes. These connections of the DLPFC receive entrances from the caudate nucleus, which compromise (destruction or interruption) manifests in pathologies such as primary (subcortical) degenerative dementias, Parkinson, and Huntington’s disease, or Huntington’s chorea. On the other hand, affectations in the basal nuclei (gray) and the PFC can be associated with obsessive-compulsive disorder\textsuperscript{15}.

Within the domain of the executive functions of the dorsolateral cortex is the ones that represent more complexity; this way, decision-making, self-evaluation, and monitoring of continuous performance, and adjustments derived from the performance of multitasking are the main characteristic of the operation that defines the DLPFC. It is this way – as mentioned above – that the dopaminergic actions have been highlighted: in aspects related to working memory and to the actions described. Certainly, dopaminergic hypofunction remarkably diminishes the quality of such complex actions. On the other hand, the OFC determines variables such as decision-making based on affective states, emotional control, affective, and social behaviors, it allows the evaluation of rewarded behaviors as well as the making of adjustments according to behavior planning and the environment, against the possibility of access to reinforcements; this is why it is closely related to the limbic system\textsuperscript{3}.

Since the first 5 years of age, the evolutionary development of the PFC presents advancements regarding executive functions; however, it is during adolescence (between 12 and 18 years of age) that it shows a high level of activation, generating its greatest process of maturation. Perhaps this development is achieved thanks to the fact that during adolescence cognitive processes are organized to achieve the legitimacy of a role in the social context and, in turn, find new ways of adaptation and growth of oneself in the environment. All this implies cerebral and cognitive development and maturation\textsuperscript{18,19}.

These variables allow cognitive control, processes that emerge in behavioral and cerebral development during adolescence. Different researches in the field of MRI-MRFI have allowed to observe this maturational process and thus recognizes that inhibition, working memory, planning, and attention are key in cognitive control. Nevertheless, it goes beyond the execution of tasks or multitasking, it allows to cover concepts such
as social cognition which are framed in different actions that allow individuals to interact with each other from perception, facial expression, body posture and gaze, representations and the ability to attribute and manipulate mental states when processing social signals.\(^{19}\)

As previously mentioned, cognitive control allows the temporal ability of organizing behavior, language, and reasoning. This enables the resolution of internal problems that respond to those representations that structure the individual from cognitive and affective integrations. Regarding the external, it refers to the conditions of interaction of the individual with the environment and the culture, dysfunctions of the executive processes associated with the dorsolateral cortex.\(^{18}\) As previously mentioned, the characteristic dysfunctions in the OFC would present difficulties to the individual when he/she modifies his/her behavior according to contingencies by virtue of access to reinforcers in the social context, and also when representing the mental states of other individuals through the recognition of verbal or non-verbal variables.\(^{20}\)

In this order of ideas, these dysfunctions are conceptually defined as dysexecutive syndromes. Delgado and Etchepareborda (2013) describe them as prefrontal syndromes, which are subdivided into three groups: dorsolateral prefrontal syndrome; orbitofrontal prefrontal syndrome; and medial prefrontal syndrome or anterior cingulate syndrome, and they attribute specific characteristics to each group. These authors agree with others in that the most common dysexecutive syndromes are related to the DLPFC. Consequently, patients with impairments in this area report difficulties in productivity and creativity but preservation of execution in repetitive tasks that do not represent a challenge – although those that require abstraction or need novelty and innovation do present disability.\(^{7}\)

These alterations hinder an individual's normal process of social adaptation in accordance with the demands of the context and the environment. Thus, difficulty in postponing behaviors and controlling impulses; detailed planning of behavior for the execution of complex activities; recognition of social cues; anticipating contingencies; self-monitoring; and modifying behavior to find reinforcers; all constitute negative sums in the individual that unleash other adjacent pathologies.\(^{7}\)

**Materials and Methods**

**Population**

Evaluation and process was made in general to 71 students (43 girls and 28 boys) between 8 and 14 years of age, most of them from public schools (59 students which represent 83% of the sample) and all of them living in stratus 1-3 (correspond to low strata that house the users with fewer resources). Selection of the sample: the exclusion criteria considered was not being in school at the moment of the study and having either a mild, moderate or profound intellectual disability. The inclusion criteria sample was made up of students schooled; it is important to mention that the minors’ legal guardians signed the informed consent, and the minors themselves agreed to participate in the study (informed assent). Moreover, this age was considered as it is the age at which it is expected to perform the chosen tests, especially the orbitofrontal tests.

Which were classified into two groups: on the one hand, children who presented school behavior difficulties and, on the other hand, children who did not. The Swanson, Nolan, and Pelham (SNAP) IV scale was applied to determine which group each child belonged to; this scale allows to identify children with significant difficulties at the attentional and behavioral levels by means of motor distress and impulsivity. It is important to clarify that although this scale is applied to identify attention deficit hyperactivity disorder both in school and at home, in this case, it was used only to determine whether difficulties arose or not, and not to perform a diagnosis as such (because it was not the objective of the research and the conditions for doing so did not take place).

**Research type and design**

The study aimed to follow a quantitative approach of a descriptive and explanatory type. It was also cross-sectional since, at a certain moment, it sought to explain the relationship between executive functions (of the dorsolateral and orbitomedial type) in children with behavioral difficulties; this was done not only from a theoretical basis but also from the analysis of other researches and the results themselves, highlighting the particularities in its operation and generating comparisons with other groups of children.

**Procedure and instruments**

The instruments used: sociodemographic data questionnaire, application of the Latin American version of the SNAP IV scale to determine the cutoff point of children presenting behavioral difficulties from those who do not and application of the Neuropsychological Assessment Battery Executive Functions Module (II), orbitofrontal (measures inhibition and regulation of
behavior) and dorsolateral (measures planning, organization, and classification) subscales/subsets.

The following (Table 1) will show the neuropsychological tests used.

This way, descriptive statistical analysis and association analysis were generated in the results. To do this, the data obtained were rigorously organized in a dynamic table designed in Excel, to favor statistical analysis. In addition, statistical programs such as Minitab and office tools such as Excel were used (since it also has relevant tools for data analysis).

### Results

Evaluation and process was made in general to 71 students (43 girls and 28 boys) between 8 and 14 years. The established protocol and in general the entire procedure of neuropsychological characterization were applied. From the analysis of the results, it has been identified that the distribution of the sample, taking into account that it is an association study, is given as follows: about 44% were cases and 56% were controls.

Part of the process is to identify and shows differences and possible associations between the two groups (case–control) to determine if it is global or if there are important differences between them. To do this, within the processing of statistical data the following have been established: at a general level make box plots to identify the distribution and concentration of data and to identify the quartiles, since it is important to remember that this is done between quartiles 1 and 3 (Q1 and Q3), and quartile 2 (Q2) is the median, that is, half of the data. The results by structural area are the following:

Although differentiated data are identified between the two groups, the control group shows greater functionality at a general level, the differences are not so marked. From the results shown in figure 1, greater differential process is evidenced in the results of Stroop form A and Stroop form B, both in time management.

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**Table 1. Neuropsychological tests used**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>General intellectual ability (GIA)</td>
<td>Raven’s progressive matrices (Raven's matrices or RPM)</td>
</tr>
<tr>
<td>Dorsolateral prefrontal cortex (DLPFC or DL-PFC) (Measures planning, organization, and classification)</td>
<td>Card sorting test, Verbal fluency</td>
</tr>
<tr>
<td>Anterior prefrontal cortex (aPFC)</td>
<td>Semantic classification</td>
</tr>
</tbody>
</table>

**Figure 1.** Box plot by orbit medial groups – comparative control case.
Likewise, at the dorsolateral level, the same process with the applied tests took place, and there is no evidence of marked differences regarding results, except for classification of letters and time management. These results are evidenced in figure 2.

However, Pearson’s Chi-squared test is carried out for association, which is a statistical process that denotes the existence of a statistically defined relationship between two variables. Now, in Chi-squared p value, fixed by convention in 0.05, means that the value should be less than this to be considered an association since it shows that the probability of a phenomenon occurring randomly is minimal. After performing the analysis, it was possible to identify where this association exists in both orbitomedial and dorsolateral, that is, table 2.

In general, the significance of the data shows that the association takes place in time management. As seen in Figure 3, all are associated with time management, with orbitomedial functions being closer.

Table 2. Statistics – Chi-squared probability ratio

<table>
<thead>
<tr>
<th>Test</th>
<th>p-value case group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orbitomedial – Stroop A (time)</td>
<td>0.042</td>
</tr>
<tr>
<td>Orbitomedial – Stroop B (time)</td>
<td>0.008</td>
</tr>
<tr>
<td>Dorsolateral classification by (time)</td>
<td>0.021</td>
</tr>
</tbody>
</table>

Discussion

According to what is shown in the results section, it is possible to see how executive functions present differentiated ranges between the control group and the analysis group. This posits differences in the way in which performance of brain activity presents itself among the different participants of the study, with grouping of the data in box plots which allows to evaluate the integration of executive functions of the orbitomedial and the dorsolateral cortex. It is also possible
to see the way executive functions behave according to different objectives or specific tasks, and therefore transfer these findings to the way in which the behavior operates in natural environments.

From this description, it can be inferred that the functionality and maturity of the orbitomedial and dorsolateral cortex are vital for normal evolutionary development and for more complex tasks such as decision-making, problem-solving, and decision-making advocated pragmatic adaptation of the individual to his/her social context. This can be seen in the application of subtests such as Stroop A and B in comparison with the control group and analysis group, since significant differences are evidenced primarily in time management because in unnoticed conditions inhibitory control is required as well as processing speed and cognitive flexibility, to escape previously established automatisms. It is a product of development and maturation of the orbitomedial cortex, which means that this is associated with the possibility of regulating, planning and modulating each step of behavior.

In the same way, another relevant analysis in the development of executive functions and the detected findings is oriented to the regulatory function of language; this seen from behavior control and direction with the help of language-oriented toward a specific goal and toward obtaining reinforcers in the natural context. Significant differences can be detected among the application of subtests such as semantic classification, where a higher performance is observed in the control group compared to the study group; although this quality belongs to the dorsolateral cortex, cold executive functions that involve planning, among others. Development and maturity of the OFC and ventromedial PFC are necessary, since it will depend to a great extent on inhibitory control and the cognitive processes involved in semantic classification tasks such as sustained attention; processing speed, cognitive flexibility, semantic memory, working memory, and the ability to suppress inappropriate responses — the latter oriented to the orbitomedial PFC.

In this order of ideas, Marino et al. (2011) reported that the pragmatic functionality of executive control — in charge of the prefrontal lobe in general terms — is oriented to perform an active search for the phonological and semantic fields for adequate and meaningful production of language, and its adaptive systematic correlation with the social environment. For this reason, inhibitory control that allows inadequate answers at the time of pragmatic production of language is necessary, as it was previously mentioned.

On the other hand, the mastery, maturity, and development of the orbitomedial PFC could explain factors related to school failure and alterations, dysfunctions or learning disorders, since adverse events in childhood can present variables of analysis on how brain activity and executive functions take place during development in childhood and adolescence, taking into account that the orbitomedial PFC matures from continuous contact with caregivers and social experience. In causality, it would be relevant to analyze these experiences during these years of development as well as the performance in tasks like those presented in this study, where the study group presents a lower performance in the subtests regarding the orbitomedial PFC.

In agreement, the findings show a lower performance of the study subjects with greater emphasis on an association of variables between cerebral activity of the orbitomedial cortex (Stroop A and B subtests) and dorsolateral cortex (Semantic Classification subtests). Consequently, it can be inferred that the study group presents lower performance in the card game, which allows to detect that there is less value in relation to risk benefit, and to the selection of behaviors related to uncertain situations.

In agreement with the different findings, especially with the study group, it can be discriminated that the fullness and efficacy of executive functions dependent on the dorsolateral cortex will depend on the maturity and development of the orbitomedial cortex. It seems that self-monitoring, the processing and regulation of emotions and emotional states, as well as the regulation and control of behavior, are essential for the development of cold executive functions with greater...
performance such as planning, operational memory, complex problem-solving, and mental flexibility.

Conflicts of interest

We declare that the authors of this research do not have and have not had conflicts of interest regarding their rights and participation, and both contributed significantly to the development of the research.

Funding

Corporación Universitaria Iberoamericana is the institution that has financed 100% of this research.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

References

Respiratory complications of amyotrophic lateral sclerosis
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Abstract
Amyotrophic lateral sclerosis (ALS) is a progressive and fatal neurodegenerative disease that inevitably affects the respiratory system, and part of its treatment focuses on improving symptoms and minimizing its respiratory complications which are the main cause of death; thus, the purpose of the following review is to describe the pulmonary involvement of ALS, to propose diagnostic/monitoring guidelines, and to expose its therapeutic options. The alveolar hypoventilation syndrome and the poor management of bronchial secretion are the main respiratory difficulties secondary to ALS and they are due to the weakness of the muscles that generate respiration; in this way, the periodic assessment of respiratory function is imperative for monitoring and detecting these complications in early stages. The care of patients with ALS should be multidisciplinary and ideally should be performed in specialized centers; non-invasive mechanical ventilation and assisted cough (manual or mechanical) are the two most cost-effective techniques to treat alveolar hypoventilation and poor secretion management to increase survival, improve symptoms, and increase quality of life.

Key words: Amyotrophic lateral sclerosis. Hypoventilation. Respiration. Artificial. Respiratory function tests.

Complicaciones respiratorias de la esclerosis lateral amiotrófica
Resumen
La esclerosis lateral amiotrófica (ELA) es una enfermedad neurodegenerativa progresiva y mortal que inevitablemente afecta el sistema respiratorio, por lo que parte de su tratamiento se enfoca en mejorar los síntomas y minimizar sus complicaciones respiratorias, que son la principal causa de muerte; así, el objetivo de la siguiente revisión es describir la afectación pulmonar de la ELA, proponer pautas de diagnóstico/monitoreo y exponer sus opciones terapéuticas. El síndrome de hipoventilación alveolar y el mal manejo de secreción bronquial son las principales alteraciones respiratorias secundarias a la ELA y se deben a la debilidad de los músculos que generan respiración. De esta manera, la evaluación periódica de la función respiratoria es imprescindible para controlar y detectar estas complicaciones en las etapas iniciales. La atención de los pacientes con ELA debe ser multidisciplinaria e idealmente debe realizarse en centros especializados. La ventilación mecánica no invasiva y la tos asistida (manual o mecánica) son las dos técnicas más rentables para tratar la hipoventilación alveolar y el manejo deficiente de las secreciones para prolongar la supervivencia, mejorar los síntomas y aumentar la calidad de vida.

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive and fatal neurodegenerative disease that has a worldwide incidence of 0.6-3.3 cases per 100,000 inhabitants. It is characterized by the death of the upper motor neurons located in the motor cortex and lower motor neurons (LMN) located in the brainstem and spinal cord1-5. The degeneration of the corticospinal axons causes thinning and scarring (sclerosis) of the lateral columns of the spinal cord and as the brainstem and spinal motor neurons die a thinning of the ventral roots and a denervation atrophy (amyotrophy) of the muscles of the tongue, oropharynx and extremities occurs, originating muscular rigidity, and spasticity; when LMN are affected, initially, they show excessive electrical irritability, producing spontaneous muscle spasms (fasciculations) but as they degenerate, they lose synaptic connectivity with their muscles causing the consequent atrophy5.

Symptoms usually begin insidiously with the involvement of a specific group of muscles, and then they progressively generalize, it should be noted that the function of the neurons of the oculomotor nuclei and Onuf’s nucleus is usually preserved until the end of the disease1-5, in approximately one-third of the cases the manifestations begin in the bulbar muscles and < 3% of the cases start directly with respiratory muscle weakness (presenting as an unexplained hypercapnic respiratory failure)1,2,8.

In Mexico, there are few data about this condition, a retrospective longitudinal study estimated a presence between 5000 and 7000 cases and described Mexican patients as usually male (male:female ratio of 1:8:1), mean age of onset 47.5 ± 10.5 years, with spinal involvement in 66% of the cases and bulbar affection in 34%, the average survival from the onset of symptoms was 68.6 months and 57.8 months since the diagnosis; 3.3% of the cases were classified as family related3,7.

The evolution of ALS to respiratory failure is inevitable and its treatment is mainly aimed to improve symptoms and minimizing the two main pulmonary complications: (1) alveolar hypoventilation (hypercapnic respiratory failure) and (2) poor management of bronchial secretions1; the objectives of the following review are to describe these complications, to propose diagnostic/monitoring guidelines, and to expose the therapeutic options available for the respiratory complications of ALS.

Effects of ALS on respiratory muscles

The physiological consequences of ALS on the respiratory system are directly secondary to the weakness of the respiratory muscles, which can be divided as follows:

- Muscles of inspiration: the muscles involved in inspiration are the diaphragm, sternocleidomastoid, scalenes, and external intercostals4; they generate the ventilation and its weakness, especially that of the diaphragm, leads to a decrease in tidal volume (amount of air entering the lung in each breath with normal effort)6; as the muscle weakness progresses, patients develop a restrictive respiratory pattern with progressive reduction of pulmonary ventilation until it ends in alveolar hypventilation and subsequent hypercapnic respiratory failure1,9; these alterations manifest as dyspnea, fatigue, orthopnea, night morning headache, nighttime choking, use of accessory muscles of breathing, and paradoxical breathing when adopting the supine position6-12.

- Muscles of expiration: the main expiratory muscles are the rectus abdominis, internal and external abdominal oblique, the transverse abdominal and the internal intercostal muscles; the decrease in the strength of these muscles generates an ineffective cough with the consequent retention of pulmonary secretions and recurrent infections4,8.

- Bulbar muscles: bulbar muscular weakness, which involves the facial, oropharyngeal, and laryngeal muscles; may affect the ability to speak, swallow, protect the lower airway, and eliminate bronchial secretions; its alteration leads to an ineffective cough, poor handling of secretions, increases the risk of aspiration and makes less tolerable the use of a non-invasive mechanical ventilation device (NIMV), vide infra; the most important symptoms secondary to this alteration are: laryngospasm, sialorrhea, dysphagia, and dysarthria8.

Evaluation of the pulmonary function in patients with ALS

Periodic assessment of respiratory function is imperative to detect early respiratory complications of ALS, these evaluations should be performed at the time of diagnosis and subsequently every 3-6 months, even in the absence of respiratory symptoms4. Respiratory function tests in patients with ALS can be classified as follows:

- Direct measurements of muscle strength are those tests that directly measure the strength of the respiratory muscles.
  - Pleural pressure: it involves the placement of a catheter in the lower third of the esophagus and connect it to a pressure transducer, it is the gold
standard for measuring diaphragmatic force; however, little is indicated because of its invasivity\(^6,11\).

- Maximum inspiratory pressure (MIP): it is a sensitive marker of diaphragmatic weakness in the early stages of ALS and correlates with survival. Normal values almost always exclude inspiratory muscle weakness and pressure lower than \(-40\) cm\(\text{H}_2\text{O}\) indicates significant inspiratory muscle weakness. When there is bulbar involvement, patients often cannot perform this procedure correctly due to the inability to form a seal around the mouthpiece (the test is done by placing a stethoscope in the mouth and doing a forced inhalation)\(^12\).

- Sniff nasal inspiratory pressure (SNIP): in this test, the sensor is placed in the nose, which avoids the need to seal the mouth, it is not affected by bulbar weakness which makes it very useful in advanced stages of the disease\(^4\). SNIP correlates adequately with transdiaphragmatic pressure. A SNIP < \(40\) cm\(\text{H}_2\text{O}\) correlates with nocturnal hypoxemia\(^13,14\), while a SNIP > \(70\) cm\(\text{H}_2\text{O}\) for men and > \(60\) cm\(\text{H}_2\text{O}\) for women excludes diaphragmatic weakness\(^15\).

- Maximum expiratory pressure: a value < \(40\) cm\(\text{H}_2\text{O}\) suggests expiratory weakness\(^4,12\).

Indirect measurements of respiratory muscle strength are those tests that measure lung volumes and flows, which indirectly represents an estimate of the strength of the respiratory muscles, especially the diaphragm:

- Spirometry: the most important parameter measured in spirometry for this group of patients is the vital capacity (VC), usually measured through a forced maneuver (forced VC) and more rarely through an unforced or slow expiration (slow VC). Hypercapnic respiratory failure is particularly common with a VC of < 15 ml/kg or an absolute value of 1 L or less\(^12\). Most centers consider a reduction of the VC of < 50% as an indication to initiate NIMV; however, the diaphragmatic weakness could be moderate or severe before the VC reaches this point\(^6,9\). The \(\Delta\)VC (VC in the sitting position - VC in the supine position) correlates very well with the diaphragm force measured by transdiaphragmatic pressure \((r^2 = 0.76, p < 0.001)\)\(^4\) and a 25% drop should be considered at as a sign of compromise the respiratory function\(^10,12\). The relationship between VC and muscle strength is not linear, so it is a sensitive marker only in moderate to severe stages of the disease, another limitation of this test is a possible incorrect sealing of the mouth which can alter the measurements\(^12\), despite this, repeated VC evaluations are an efficient way to detect respiratory muscle weakness making it a simple, accessible and reliable follow-up test\(^6,13\).

- Peak cough flow (PCF): it is done with a peak flow meter that is placed in the mouth (requires mouth sealing and is useful when there is bulbar integrity) or through a mask (do not require oral sealing and is used in the presence of bulbar impairment) and the patient is asked to cough heavily on three occasions, taking into account only the highest value, a value < \(270\) L/min means that the cough is ineffective and indicates the need to implement assistance techniques for cough, while < \(160\) L/min predicts respiratory failure\(^9,12\).

- Gas exchange tests: arterial blood gas analysis is the only gas exchange test useful in patients with ALS and should be performed in all patients; in advanced stages of the disease it is the best indicator of the need for mechanical ventilation when there is a confirmation of a decrease in Pa\(\text{O}_2\) and the elevation of Pa\(\text{CO}_2\) and HCO\(_3\)\(^4,12,14\).

- Sleep studies: between 17% and 76% of patients with ALS have a respiratory sleep disorder, the most frequent and feared alteration is the sleep-related hypventilation syndrome; however, it must be considered that patients with bulbar affection have a high risk of obstructive apneas, figure 1. Sleep studies in patients with ALS can be summarized as follows:

  - Polysomnography (PSG): it is the gold standard technique for diagnosing sleep disorders of breathing in patients with ALS, the suggested signals to record in this group of patients include: electroencephalogram, electro-oculogram, chin electromyography, snoring, respiratory flow-through two channels (nasal pressure cannula and oronasal thermal sensor), respiratory effort (band in chest and abdomen, ideally inducance plethysmography), electrocardiogram (DII), pulse oximetry, carbon dioxide (can be transcutaneous or exhaled), tibialis anterior electromyography, and body position. Internationally, hypventilation during sleep is

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**Table 1. Definition of hypoventilation during sleep adjusted to moderate altitudes**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong> Elevation of PC(_2) (or a surrogate) &gt; 50 mmHg for 10 min</td>
<td>Hypoventilation during sleep adjusted to moderate altitudes</td>
</tr>
<tr>
<td><strong>B</strong> Elevation &gt; 10 mmHg of PC(_2) (or a surrogate) during sleep</td>
<td>Hypoventilation during sleep adjusted to moderate altitudes</td>
</tr>
</tbody>
</table>

The patient can meet any of the two criteria.

mmHg: millimeters of mercury, PC\(_2\): carbon dioxide pressure.
defined when the PSG meets any of the following criteria: (a) an elevation of PCO$_2$ (or a surrogate) $> 55$ mmHg for 10 min, or (b) an elevation $> 10$ mmHg of PCO$_2$ (or a surrogate) during sleep, compared to the awake and supine value, up to a value $> 50$ mmHg for 10 min; this definition is

Figure 1. We present the case of a 56-year-old woman diagnosed with ALS with bulbar disease, sent to our service for habitual and intense snoring, witnessed apneas, and excessive daytime sleepiness. The patient presented 26 points on the Bulbar Affectation Scale of Norris, the gasometry in wakefulness was normal and she presented a peak cough flow measured with a mask of 290 L/min. **A:** Image of polysomnography compacted at 2 min with an increased superficial sleep (N1 and N2), decreased R, and obstructive sleep apneas. **B:** Transcutaneous capnography obtained during polysomnography, the ventilation during the study was normal. **C:** Therapeutic test with a bilevel ST positive pressure equipment programmed in the outpatient clinic, a stable flow curve and the optimum residual hypopnea apnea index are observed. AHI: apnea hipopnea index; AI: arousal index; CA: central apneas; HIP: hypopneas; MA: mixed apneas; mmHg: millimeters of mercury; N: no rapid eye movements sleep; OA: obstructive apneas; R: rapid eye movement sleep; RR: respiratory rate; TCCO$_2$: transcutaneous carbon dioxide; TC90%: < 90% saturation time expressed as % of TST; TST: total sleep time; T > 45 mmHg: time in minutes with TCCO$_2$ > 45 mmHg.
Table 2. Essential pulmonary function tests in the follow-up of patients with ALS

<table>
<thead>
<tr>
<th>ALS without bulbar affection</th>
<th>ALS with bulbar affection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spirometry + maximum inspiratory pressure</td>
<td>Sniff nasal inspiratory pressure</td>
</tr>
<tr>
<td>Gasometry</td>
<td>Gasometry</td>
</tr>
<tr>
<td>Peak cough flow with mouthpiece</td>
<td>Peak flow of cough with mask</td>
</tr>
</tbody>
</table>

ALS: amyotrophic lateral sclerosis.

- Night capnography: currently, there are capnography devices with transcutaneous measurement, which also incorporate pulse oximetry, which could be useful for diagnosing hypoventilation during sleep, figure 1; however, its diagnostic performance has not been evaluated; at this time, its best indication is as follow-up once the NIMV has been started.

The pulmonary function tests indispensable in patients with ALS are summarized in table 2.

Treatment of respiratory complications of ALS

The therapeutic options for modifying the disease are limited; currently, riluzole and edaravone are the only two drugs authorized by the U.S. Federal Drug Administration to reduce deterioration and slow down the progression of ALS, so, much of the therapy focuses on the management of respiratory complications.

Treatment of alveolar hypoventilation

NIMV

In patients with ALS, respiratory muscle disease with progression to alveolar hypoventilation is unavoidable and cost/benefit its best treatment is NIMV, which prolongs survival and improves symptoms and quality of life. The best moment to initiate NIMV is when there is hypercapnia (hypoventilation) at night with diurnal eucapnia, so waiting for the onset of daytime hypercapnia to initiate NIMV may be a risk factor to develop acute respiratory failure, but, starting the NIMV in the absence of symptoms or nocturnal hypoventilation may not offer benefits, however, predicting this exact moment of nocturnal hypercapnia with diurnal eucapnia can be difficult, possibly the best way to diagnose it is with serial gasometries and PSGs; however, this may not be accessible, in such a way, the respiratory function tests can be very useful, in the absence of PSG, the indications to initiate NIMV in patients with ALS are:

- Symptoms: mainly dyspnea and orthopnea.
- VC < 50% of predicted or an accelerated decrease rate.
- MIP < – 60 cmH₂O.
- SNIP < – 40 cmH₂O.
- PaCO₂ > 45 mmHg in wakefulness.

The ventilatory support is usually started at night with the objective that NIMV assumes the work of breathing during sleep. Inspiratory and expiratory pressures are assessed to maintain a tidal volume of 12-15 ml/kg of

adequate when the study is carried out at sea level, but it must be considered that this definition requires adjustment for moderate altitudes such as Mexico City, table 1. The most reported alteration in sleep architecture among patients with ALS is the decrease in the percentage of rapid eye movement (R) with increased in N1 stage (non-rapid eye movement), which has been associated with decreased survival. The R stage of sleep represents a period of vulnerability for the respiratory mechanics of patients with ALS and is usually the initial moment for the respiratory complications, since muscular atony occurs with loss of the contribution of the respiratory accessory muscles over the tidal volume and the diaphragm is the sole driver of ventilation, this weakness can cause severe alveolar hypoventilation that leads to sustained desaturation and hypercapnia.

- Respiratory polygraph or simplified sleep study: consists of recording only cardiorespiratory variables during sleep, the most used are: respiratory flow, effort, snoring, pulse oximetry, heart rate, and body position, eliminating sleep stages; however, they also do not allow the measurement of CO₂, their role in the diagnosis of respiratory disorders of sleep in patients with ALS is limited.
- Nighttime oximetry: it is the most available sleep test, it detects desaturation events; however, it cannot provide information about ventilation and sleep architecture; it has been found abnormal nocturnal oximetry in 40% of patients with ALS without respiratory symptoms, normal respiratory function tests, and normal electrodiagnostic tests of the phrenic nerve and diaphragm. Nocturnal desaturation correlates with inspiratory muscle weakness and can be used as a guide to initiate NIMV in the absence of PSG; it has been reported that patients who start using NIMV based on nocturnal desaturation can improve their survival.
At the end, patients will need continuous ventilatory assistance (homecare). Once the progressive bulbar weakness prevents the ability of patients to eliminate their secretions (even with mechanical assistance), NIMV is no longer a viable treatment option, so the decision should be made to proceed with the tracheostomy or concentrate in palliation⁴.

**IMV and care at the end of life**

IMV through a tracheotomy is an option in specific circumstances:
- When NIMV is not able to maintain adequate ventilation due to the progression of the disease.
- If the use of NIMV is required during most of the day and night (> 16 h/day).
- Bulbar muscular deterioration that does not allow a tolerance of NIMV, with a deficient control and elimination of secretions that are not improved by pharmacological strategies and mechanically assisted coughing techniques.
- When the patient wants to maximize their survival⁴,⁸,¹⁰. IMV is strongly associated with prolonged survival in ALS; however, an improvement in quality of life is less clear, patients with tracheotomy continue to experience progression of the disease, so some patients eventually progress to a state without communication or movement⁴.

It is important that patients and family members recognize that the care required by patients with IMV at home is complex, at least two highly trained and motivated family members are needed for special care of the stoma, hygiene of the cannula, and correct aspiration technique of secretions; therefore, the IMV in these patients causes an increase in the cost of treatment, with significant emotional and social impact on both the patient and their caregivers, and can reduce the quality of life of both⁴,⁶.

Given that the ALS has a predictable course, it is important to discuss with the patients and caregivers the possible invasive and non-invasive management options as soon as possible, with the aim of avoiding these decisions in the context of an abrupt clinical deterioration and giving them, patients and relatives, the time to reflect; the decision to perform a tracheotomy should only be taken with the informed consent of the patient and after a careful discussion about its pros and cons⁴,⁸,⁲³.

**Diaphragmatic pacemaker**

The use of diaphragmatic pacemakers has been investigated as a way to reduce the decline in lung function; however, randomized studies reported an increase

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**Table 3. Programming of equipment for initial NIMV**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ALS without bulbar affectation</th>
<th>ALS with bulbar affectation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode</td>
<td>Bilevel ST</td>
<td>Bilevel ST</td>
</tr>
<tr>
<td>RR (rpm)</td>
<td>14 a 20</td>
<td>14 a 20</td>
</tr>
<tr>
<td>EPAP o PEEP (cmH₂O)</td>
<td>4 a 6</td>
<td>6 a 8</td>
</tr>
<tr>
<td>PS (cmH₂O)</td>
<td>6 a 8</td>
<td>6 a 8</td>
</tr>
<tr>
<td>Tigger</td>
<td>High or very high</td>
<td>High or very high</td>
</tr>
<tr>
<td>Cycling</td>
<td>Medium or high</td>
<td>Medium or high</td>
</tr>
</tbody>
</table>

ALS: amyotrophic lateral sclerosis; EPAP: expiratory positive airway pressure; PEEP: positive end expiratory pressure (synonymous with EPAP); PS: pressure support; RR: respiratory rate; ST: spontaneous/time; NIMV: non-invasive mechanical ventilation.
Management of bronchial secretions in patients with ALS

An essential mechanism of protection of the airway is the ability to cough when the clearance of bronchial secretions is impaired; this represents a serious threat to life. Effective cough initially requires full inspiration, followed by a glottal closure and by last an intense contraction of the expiratory muscles to generate adequate pressures and flows to move the bronchial secretions; these phases can be affected in different ways and in different magnitudes in all the neuromuscular diseases; however, in ALS the affliction at three phases are progressive and severe; thus, the diaphragmatic weakness will decrease the initial inspiration (this is the condition that takes longer to appear), the bulbar alteration will deteriorate the glottic closure and the weakness of the rectus abdominis, obliques, and internal intercostals will wear out the expiratory phase (it is usually the initial alteration). Physical therapy such as percussion or other techniques to mobilize secretions is not enough in patients with ALS. Cough assistance techniques are indicated when patients’ PCF falls below 270 L/min; these techniques can be classified as follows:

- Manually assisted cough: manual cough should be considered in patients with conserved glottic function, since artificial inspiratory flows and assisted abdominal movements replace the respiratory muscles, but nothing can replace glottic function; this technique is carried out in a simple way following this steps:
  - With a bag-valve-mask ventilation device (Ambu) several assisted breaths are made, asking the patient to retain the air in each of them with the objective of expanding the lung close to total lung capacity (the maximum amount of air inside the thorax after a forced inspiration); then, the patient will cough but will use an abdominal push to increase the intra-abdominal pressure and exhale forcefully; this push can be exercised by an assistant directly with their hands on the abdomen of the patient.
  - It is common for bronchial secretions to remain in the pharynx or mouth from where they will have to be extracted with a vacuum.
  - Mechanical techniques: mechanically assisted cough or mechanical insufflation-exsufflation (MIE) is the most effective alternative in these patients to avoid the accumulation of bronchial secretions, it is especially indicated when the PCF is < 160 L/min; it is performed with a mechanical device that accumulates several breaths with positive pressure before suddenly changing to a negative pressure:
    - An oronasal mask or tracheotomy connector is placed and positive pressure is applied; the applied pressure can vary between +20 and +40 cm H₂O.
    - To simulate a normal cough, the pressure is suddenly changed to negative values, the pressure generated in this phase can vary between –20 and –40 cm H₂O.
    - Some MIE equipment incorporates oscillatory waves to fluidize secretions.
    - It is common for the bronchial secretions to remain in the pharynx or mouth from where they will have to be extracted with a vacuum.
    - 6-8 MIE cycles per session should be administered.

Isolated symptoms and special situations

Sialorrhea

Sialorrhea among patients with ALS is common, can be socially disabling and hinder the use of NIMV. It can be treated with oral suction or with pharmacological measures through medications with mild antimuscarinic effect such as oral glycopyrrolate (2-8 mg/day), anticholinergic (75-150 mg/day), and transdermal scopolamine patch (1.5-3 mg/72 h) among others; if an acceptable therapeutic effect is not obtained, injection of botulinum toxin into the salivary glands can be used; however, as the toxin can spread to nearby muscles, it can worsen dysphagia and should be reserved only for gastrostomy patients; another option to consider is the use of local radiotherapy, which has fewer side effects, but does not last as long as botulinum toxin.

Dyspnea

Although there are no clinical trials of the management of dyspnea in ALS, the recommendations for the control of it arise from the clinical contexts where dyspnea is a characteristic symptom of the disease in its terminal phases and is an integral part of management in palliative care. For distressing dyspnea, first-line drugs are systemic opioids, which can be indicated from the onset of the symptom and not only in the final stage of the disease. Treatment begins with an initial dose...
equivalent to 2.5 mg of morphine sulfate every 4 h. The dose should be increased by 30% every 12 h until dyspnea improves or intolerable side effects develop. When an adequate relief of symptoms is obtained, the use of a long-acting opiate such as oral or transdermal fentanyl is recommended. For exacerbations of dyspnea, doses of recap are used, which are 10% of the total daily dose administered as needed each hour for oral medications or every 30 min for parenteral medications.

**Vaccination**

Vaccination against influenza and pneumococcus is recommended following the corresponding schemes.

**Oxygen**

Patients with early respiratory failure should not be treated with oxygen without other forms of ventilatory support (NIMV or IMV), since oxygen therapy in respiratory failure suppresses the hypoxic drive and increases the risk of hypercapnia.

**Acute respiratory failure**

Despite the lack of randomized controlled studies, there is agreement on the effectiveness of NIMV to prevent endotracheal intubation in acute respiratory failure events, thus, in one study, three out of four patients who had previously rejected the tracheotomy, but not the NIMV they survived an episode of acute respiratory failure treated with NIMV; the factors associated with success are the correct programming of the ventilation devices, the availability of several types of interfaces (masks) and the proper management of secretions; the main factor limiting the success of NIMV during a respiratory infection is the severity of bulbar dysfunction with a cutoff point on the Norris Scale of 12 points (sensitivity 0.90, specificity 0.92, positive predictive value 0.76, and negative predictive value 0.97).

The complete pulmonary complications of ALS and their treatments are summarized in table 4.

**Follow-up**

The care of patients with ALS should be multidisciplinary and ideally should be performed in specialized centers involving: neurologists, pulmonologists, otorhinolaryngologists, rehabilitation physicians, psychologists, and psychiatrists among others; all with the common goal of increasing survival, improve quality of life, and decreasing hospitalizations from acute events; these specialized centers usually offer appointments with different specialists in a single visit, reducing the trips of patients to the hospital and, consequently, their fatigue. Quarterly appointments are usually proposed, with variations according to the progression of the disease.

**Conclusions**

The respiratory complications of ALS represent a serious problem for people with this disease and are secondary to the weakness of the muscles that generate respiration; non-IMV and assisted cough (manual or mechanical) are the two most cost/effective techniques to treat alveolar hypoventilation and poor secretion management, respectively, these tools used in conjunction prolong survival and improve the quality of life of the patients with ALS.
**Conflicts of interest**

All authors of the manuscript declare no conflicts of interest or relationship with the pharmaceutical industry.

**Funding**

This manuscript has no external funding source.

**Acknowledgments**

We thank the Latin American Association of Thorax (ALAT) and the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) for the grant to Monserrat Evelia Arroyo Rojas.

**Ethical disclosures**

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

**References**

Neurotoxicity of calcineurin inhibitors: Tacrolimus

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Abstract

At the beginning of this century, calcineurin inhibitors, especially tacrolimus, were the treatment of choice for immunosuppression in solid organs. It is known that in recent years, the incidence of renal and hepatic transplants has increased up to 15%, and therefore, a compelling reason why immunosuppression treatment is more relevant to reduce rejection, morbidity, and mortality rates. Although the systemic complications of the use of calcineurin inhibitors are known, there is still little information on its neurotoxic effects; however, a prevalence in up to 28% is estimated with a broad spectrum of clinical and radiological manifestations. The relevance of this work lies in describing the phenomenon of neurotoxicity, its clinical and radiological manifestations, risk factors, and management.

Key words: Neurotoxicity. Tacrolimus. Tremor. Transplant.

Introduction

Tacrolimus (FK-509 or fujimycin) is a macrolide inhibitor of calcineurin which limits the signaling of T lymphocytes and transcription of IL-2; therefore, it is a pillar in the treatment of immunosuppression after the transplant of solid organs worldwide, confirming the protocol Elite-Symphony in 2007.

The toxic effects related to calcineurin inhibitors are mostly metabolic (hypercholesterolemia and hyperglycemia), nephrotoxic, hematological, and neoplastic and infectious alterations.
Neurological complications have been the least studied despite presenting a relevant prevalence between 10 and 28%, containing a broad spectrum of manifestations ranging from mood changes to coma⁴. In the review of the literature, there is limited information and not a lot of studies conducted to assess the neurological complications in this group. Muller et al.³ described post-operative neurological complications due to the use of tacrolimus in post-transplant liver patients.

It has been reported that the risk factors for developing neurological complications are hepatic failure, systemic hypertension, hypocholesterolemia, and high levels and concomitant use of methylprednisolone. However, it should be noted that many of the risk factors and complications present difficulties in establishing causality since many of these patients have multiple comorbidities and use other immunosuppressants².

Although the association of neurological complications and tacrolimus is known, comparative studies between transplants of different organs in the long term are not yet available.

Tacrolimus has a great variability in its interindividual pharmacokinetics, so traditional dosing schemes are often obsolete and must be individualized from patient to patient. Therefore, constant monitoring of serum levels is important. It is known that reaching adequate serum levels is essential in the post-transplant period to avoid rejection, but it is still unknown at what speed and neurotoxic levels⁴.

The metabolism of tacrolimus is mainly hepatic in cytochrome P450 3A5, so alterations in this cytochrome can cause an erratic bioavailability, but it has been seen that the levels of hematocrit, weight, and use of steroids can also interfere⁵.

It has been observed that during the 1st year post-op, serum levels can change despite maintaining the same doses, therefore, up to 60% of patients will have non-therapeutic doses. Most physicians will establish the dose based on their clinical experience and will not use different tools designed for this purpose such as the use of specialized programs or measurement of CYP3A4⁴.

**Neurotoxicity**

As previously mentioned, neurological complications can be found in up to 28% of the transplanted patients, but characteristics will differ depending on the transplanted organ and serum levels.

There is also a lack of evidence of the use of calcineurin inhibitors in the different transplanted organs, and therefore, a failure in the prevention of complications, in addition to the lack of follow-up in long-term complications. In the case of kidney transplantation, up to 60% of patients have tremor during their follow-up appointments⁷.

It is suggested that the mechanism of the neurotoxic effect is based on selected toxicity to glial cells and induction of oligodendrocyte apoptosis, but the clinical manifestation will depend on the time and severity of the exposure⁸.

Complications can be divided according to their severity: mild, moderate, and severe. Not only the most frequent manifestation that we can find is tremor, followed by headache, but also manifestations of both the central and peripheral nervous systems are frequently found (Table 1).

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremor</td>
<td>Visual alterations</td>
<td>Coma/Altered consciousness</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>Cortical blindness</td>
<td>Confusion</td>
<td></td>
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<tr>
<td>Mood alterations</td>
<td>PRES</td>
<td>Psychosis</td>
<td></td>
</tr>
<tr>
<td>Neuralgia</td>
<td>Apraxia of speech</td>
<td>Seizures</td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Leukoencephalopathy</td>
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</table>

Less severe symptoms such as tremor or paresthesia can last months to years and revert spontaneously. Some of the more severe complications, such as visual blindness, are associated with an abrupt increase in tacrolimus levels. Multiple reports of paraplegia, symmetric polyneuropathy, dysarthria, and encephalopathy have been also reported in the literature.

Unlike kidney transplantation, a greater number of complications have been observed in liver transplantation, due to different mechanisms such as alteration in metabolism and circulating metabolites. The most frequent manifestations in these patients are alterations in the state of consciousness and seizures, and usually more severe manifestations⁹.

**Sympathetic system**

One of the most frequent complications of the use of tacrolimus is systemic arterial hypertension, but it is a consequence of a sympathetic dysfunction, possibly
due to a modulation of NMDA and GABA receptors and modulating pre- and post-synaptic glutaminergic receptors

Clinical impact

In patients, a decrease in quality of life and an increase in morbidity and mortality have been observed, especially in liver transplant patients. In the first instance, severe complications can increase risk of death, but moderate complications can result in transplant rejection. Furthermore, systemic hypertension being a frequent complication results in cardiovascular and cerebrovascular risks. It is important to note that some of the complications will not be reversible.

Image studies

The diagnostic standard is MRI, its indication focuses on moderate-to-severe complications such as in the case of seizures, altered state of consciousness, cortical blindness, and speech alterations. There are no prospective studies of the alterations by imaging, but a predilection for involvement of the white matter in the occipital region has been observed. In post-liver transplant patients, pontine and extra-pontine myelinolysis have also been identified (Fig. 1).

Management and treatment

The broad spectrum of manifestations should be treated first in a symptomatic way, and studies on serum levels should be carried out at the same time, also electrolytes should be measured, monitoring blood pressure, and evaluating imaging or neurophysiological studies are highly recommended.

If the serum levels are high and mild-to-moderate manifestations, the dose can be gradually decreased and the response assessed, while in severe symptoms the most appropriate is the suspension and adjustment of immunosuppression.

In the symptomatic treatment, the use of anticonvulsants, phenytoin, phenobarbital, and carbamazepine should be avoided since having the hepatic metabolism, serum levels might become erratic. Although empirically, the use of valproic acid and levetiracetam is recommended. Finally, it is recommended to control blood pressure levels and electrolyte alterations, mainly magnesium, which is a factor for the development of seizures.

Conclusions

Tacrolimus is essential in the treatment of immunosuppression in the transplantation of solid organs, but its neurotoxic effects have a significant impact on the morbidity and mortality of patients. Patients with liver transplantation should be more vigilant because of the number of complications and severity.

In Mexico, as in the rest of the world, the rate of transplants is increasing, so these complications will become more frequent, and protocols for surveillance, prevention, and treatment must be developed.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

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