Clinical implications of cognitive impairment and alcohol dependence

Deterioro cognitivo y dependencia alcohólica, implicaciones clínicas

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The fact that the use and abuse of alcohol damages brain tissue, and therefore its functions, has been known for a long time at both clinical and research levels (Bates, Bowden & Barry, 2002; Naim-Feil, Fitzgerald, Bradshaw, Lubman & Sheppard, 2014; Stavro, Pelletier & Potvin, 2013; Wilcox, Dekonenko, Mayer, Bogenschutz & Turner, 2014; Wollenweber et al., 2014). However, there is an ongoing debate about how this damage occurs and what consequences it has on alcohol withdrawal treatment (Horton, Duffy, Hollins Martin & Martin, 2015). Moreover, it is undervalued and not taken into account in healthcare settings where patients are treated for problems related to alcohol use (Horton et al., 2015), although it is estimated that between 9 and 22% of patients diagnosed with dementia abuse alcohol, and dementia is present in 10-24% of alcohol abuse patients (Ridley, Draper & Withall, 2013).

In alcohol-related brain damage (ARBD), two main neurotoxic dimensions are combined which will determine the degree of damage present in each individual, and whether or not this damage falls into the category of dementia (Moretti, Caruso, Dal Ben, Gazzin & Tiribelli, 2017):

Direct neurotoxic effects of alcohol: periods of binge drinking followed by periods of abstinence produce a neurotoxic effect mediated by glutamatergic excitotoxicity (induced through up-regulation of NMDA receptors), a kind of kindling (Golpe, Isorna, Barreiro, Braña & Rial, 2017; Vargas-Martinez, Trapero-Bertran, Gil-Garcia & Lima-Serrano, 2018). Such neuronal damage would be more intense at the level of the hippocampus, hypothalamus and cerebellum, which affects memory and learning capacity (Ridley et al., 2013). Furthermore, the cholinergic function would be affected by this excitotoxicity, leading to increased attention, memory and learning disorders (Ridley et al., 2013). Another area deeply affected is the prefrontal cortex, with subsequent executive dysfunction. Alcohol also appears to be capable of causing brain damage through apoptosis, oxidative stress, mitochondrial damage and altered neurogenesis (Sachdeva, Chandra, Choudhary, Dayal & Anand, 2016).

Thiamine deficiency: poor nutrition, malabsorption in the digestive tract, and liver failure present in patients with alcohol dependence determine the onset of a severe condition: Wernicke's encephalopathy (WE), which, if left untreated, can become chronic and give rise to Korsakoff's syndrome (KS) (Horton et al., 2015). WE is characterized by a confusional state, with vision and gait disorders. KS is characterized by severe anterograde and retrograde amnesia, space-time disorientation, apathy and executive dysfunction, and anxiety; and although most patients improve, an estimated 25% will require chronic residential care (Horton et al., 2015). Such patients present deterioration in social and work lives going beyond mere amnesia and clearly reaching the category of dementia. Neuroimaging studies indicate the presence of damage in diencephalic subcortical structures (thalamus, cerebellum, mammillary

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bodies) and cortical structures (frontal, parietal and cingulate). The combination of both states (WE + KS) is present in 1-2% of all autopsies, and in 10% of those carried out on alcohol abusers (Ridley et al., 2013).

Brain damage associated with these two neurotoxic dimensions, a marked cerebral atrophy with white matter damage and neuronal destruction (Erdozain et al., 2014), is widespread among patients with problems linked to excessive alcohol use and is detected in up to 78% of autopsies (Ridley et al., 2013). In the clinic, a combination of brain damage caused by both dimensions is usually found (Moretti et al., 2017; Ridley et al., 2013; Zahr & Pfefferbaum, 2017) which seems to severely damage the white matter of the prefrontal cortex, the corpus callosum and the cerebellum, and produce neuronal damage in the prefrontal cortex, hypothalamus, and cerebellum (Zahr & Pfefferbaum, 2017). Overall, patients diagnosed with KS present lesions and thus a more severe deterioration in comparison with those that only present damage associated with the direct neurotoxic effects of alcohol (Hayes, Demirkol, Ridley, Withall & Draper, 2016).

Alterations in white matter are partially reversible if prolonged alcohol abstinence can be achieved to allow the restoration of adequate myelination and axonal integrity (Ridley et al., 2013). This recovery would be accompanied by an improvement in cognitive and motor functions. Recovery speed is slow, especially for executive functions, and is linked to the duration of abstinence and the intensity of alcohol use prior to it, rather than to total lifetime use (Ridley et al., 2013). The accumulation over the lifespan of binge drinking episodes followed by withdrawal syndromes, leads to slower and less complete recovery since it produces greater brain damage and with it more cognitive deterioration. This is why lifetime alcohol use is not a risk factor for cognitive deterioration in low-risk users but rather for abusers and dependents (Woods et al., 2016). It is not a question of how much alcohol has been drunk over a lifetime but rather how it has been drunk.

Women appear to be more susceptible to the neurotoxic effects of alcohol and recover more slowly. A higher level of educational attainment seems to exert a protective effect, which could reflect either a better premorbid cognitive level or a greater cognitive reserve achieved through intellectual activity, or both (Ridley et al., 2013). Since all brain structures suffer progressive deterioration with age, when assessing the damage produced by alcohol, age is a confounding factor that should be controlled for with reference values for each age group (Hayes et al., 2016).

After two years of abstinence, both improvement and deterioration stabilize, unlike in other pathologies related to brain damage (Ridley et al., 2013). It is estimated that brain damage caused by thiamine deficiency is more likely to lead to chronification than direct damage produced by alcohol (Sachdeva et al., 2016). If the overall alcohol use in the population is taken into account, a situation similar to that of cardiac risk is observed, yielding a J-shaped risk curve. Light drinking of less than 20 grams of ethanol per day could have a protective effect at the cognitive level, while abusive consumption produces a deterioration (Sachdeva et al., 2016).

When these alterations become chronic and intensify, they enter the dementia spectrum; it is estimated that such cerebral damage is present in 10-24% of the dementia diagnoses in residents of centers for the elderly, reflecting its widespread prevalence, with people under 60 most affected (Ridley et al., 2013).

Unfortunately, patients may present further brain damage associated with a lifestyle which harbors other risk factors, for example traumatic brain injuries due to accidents or violence, the consumption of other toxins, and vascular damage. In addition, given the high comorbidity of psychiatric disorders suffered by patients with alcohol dependence, they can present brain damage accompanied by cognitive deterioration, which is typical of these disorders. A clear example would be depression (Sachdeva et al., 2016)

Assessment of brain damage associated with alcohol use

There are numerous neuropsychological tests that have been used to measure ARBD. According to Aharonovich et al. (2018), the most widely-used are a measurement of global intelligence through the Wechsler scale (WAIS) and its subscales, the FAS verbal fluency test, memory tests such as the WAIS or Rey's complex figure, attentional tests such as the Stroop test or the Trail Making Test (TMT), executive function tests such as the Wisconsin Card Sorting Test (WCST), and even screening tests for dementia such as the Mini Mental State Examination (MMSE) which are not very specific for this type of patient, or others with more validity when used with substance users, such as the ACE-R (Addenbroke's Cognitive Assessment-revised) or the MoCA (Montreal Cognitive Assessment) (Hagen et al., 2016; Hayes et al., 2016).

Although the use of these tests has been heterogeneous and different authors have combined them in non-systematic and non-validated ways, an abundance of studies indicate the presence of disorders in the following cognitive functions: anterograde memory, executive function (decision making, temporal orientation, emotional judgments and verbal fluency) and visuospatial tasks. Working memory and latency time are generally affected. The question as to which cognitive functions are most seriously affected depends on how the two dimensions outlined above , direct damage and thiamine deficiency, interact with the risk factors in each patient (Maharasingam, Macniven & Mason, 2013). Despite the intensity of these disorders, it is estima-

ted that the overall intellectual functioning of these patients is reasonably well preserved, particularly at the level of language, above all when compared to the development of degenerative and vascular dementias (Horton et al., 2015; Ridley et al., 2013; Sachdeva et al., 2016). All affected functions improve after a year of abstinence, with damage to anterograde memory, the most closely linked to thiamine deficit, being the most persistent (Sachdeva et al., 2016).

Cognitive assessment is thought to be appropriate between 1 to 6 weeks after achieving abstinence from alcohol, although some authors recommend 60 days of abstinence first (Hayes et al., 2016).

Consequences of cerebral damage associated with alcohol use

The interference which cognitive damage can cause to the treatment process for achieving alcohol abstinence is of particular concern. Patients with ARBD have motivational and treatment adherence problems derived from their cognitive disorders. Additionally, certain psychotherapeutic procedures such as cognitive and behavioral ones may be affected and their effectiveness diminished due to memory and executive function disorders presented by patients (Sachdeva et al., 2016).

Furthermore, even in its mild forms ARBD may not only affect the treatment of alcoholic withdrawal but also the habits that affect patients' health; it is thus recommended that all patients with problems related to alcohol use are assessed only once they are abstinent, as previously indicated (Hayes et al., 2016).

Treatment of cerebral damage associated with alcohol use

Obviously, the best tool for avoiding ARBD is prevention. Reducing global consumption in the population, delaying the age of alcohol onset and insisting on the treatment of those who already present problems of alcohol abuse are fundamental measures.

Moreover, at the slightest suspicion of WE, a treatment with parenteral thiamine should be administered (up to 1 gram for the first 24 hours of treatment, since it is not effective orally); this can reverse the condition if the treatment starts within the first 48-72 hours. It is also advisable to balance potassium and niacin levels (Sachdeva et al., 2016). Treatment with parenteral thiamin should be continued for 5 days, followed by oral supplementation of 300 mg per day for several weeks (Hayes et al., 2016).

Cognitive remediation is a potentially useful therapeutic tool in patients with ARBD. Studies to date, although not numerous, have yielded improvements in attention, working and episodic memory (Hayes et al., 2016; Sachdeva et al., 2016; Svanberg & Evans, 2013), which appear to have an effect when it comes to improving the capacity for social interaction and consolidating abstinence (Frias-Torres et al., 2018; Hayes et al., 2016). Although the results are not yet powerful enough to make a definitive recommendation, it is possible that boosting the cognitive function of patients with ARBD improves their ability to remain abstinent and is, therefore, a necessary intervention (Bates, Buckman & Nguyen, 2013).

Compensatory psychosocial Interventions in the rehabilitation of patients with ARBD have also been shown to be effective. Such interventions focus on solving everyday problems through the programming of daily activities with the help of professionals and family. Facilitators such as diaries and alarms are used to set the patient's daily activities and to make up for mnemonic deterioration (Hayes et al., 2016).

Memantine, an antagonist with low affinity for the NMDA receptor which is recommended for degenerative dementia, has shown promising results in patients with alcoholic dementia, with improvements in overall cognitive function and quality of life, and a reduction in behavioral disorders. (Sachdeva et al., 2016).

Conclusion

In conclusion, it could be said that brain damage produced by alcohol abuse (ARBD) is scaled, ranging from mild deterioration to dementia. In any case, ARBD worsens treatment response and patient progress. ARBD is associated with two dimensions which usually interact in all cases and are also scaled: the direct neurotoxicity of alcohol linked especially to glutamatergic excitotoxicity and associated with episodes of binge drinking and subsequent abstinence; and on the other hand, thiamine deficit, which gives rise to the WE-KS complex and tends to involve greater severity. ARBD appears to severely damage the white matter of the prefrontal cortex, the corpus callosum, and the cerebellum, and produce neuronal damage in the prefrontal cortex, hypothalamus, and cerebellum. However, ARBD is reversible if a prolonged alcoholic withdrawal of at least 1-2 years can be achieved.

ARBD is associated with disorders in the following cognitive functions: anterograde memory, executive function (decision making, temporal orientation, emotional judgments and verbal fluency) and visuospatial tasks, working memory and latency time. While no battery of cognitive tests validated for ARBD is currently available, it is considered necessary that such a battery cover all the functions that may be susceptible to disorder, and it is recommended that all patients at risk of presenting ARBD be evaluated once they have consolidated a period of abstinence of at least one week.

To date there is no pharmacological or remediation treatment approved for ARBD. Alternatives such as cogni-

tive remediation, psychosocial rehabilitation and memantine have yielded promising preliminary results.

Conflict of interests

The authors declare no conflict of interest for the present study.

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