FASD and ADHD: a review on executive functions and treatment

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Abstract

Although the teratogenic effects of alcohol have been known for years, the prevalence of disorders caused by alcohol consumption during pregnancy is still high. The term Fetal Alcohol Spectrum Disorders (FASD) encompasses the different versions of this disorder, which leaves a substantial trace of cognitive difficulties. Among the many disorders that have a high comorbidity with FASD, Attention Deficit Hyperactivity Disorder (ADHD) presents one of the highest rates. Despite many years of research, the relationship between FASD and ADHD remains unclear. This review summarises the latest findings on FASD/FASD-ADHD treatment whilst emphasising the differences between the two disorders regarding executive functioning. In fact, it has been found that people with FASD do not respond to medication for ADHD in the same way as individuals with just ADHD. Furthermore, there is little information on non-pharmacological treatments that improve executive functions in individuals with FASD. Recent studies determine that cognitive training achieves the best results, especially when combined with other therapies such as Animal-Assisted Therapy (AAT), transcranial stimulation and family interventions.

Key words: FASD, ADHD, comorbidity, pharmacological treatment, non-pharmacological treatment, executive functions.

Resumen

Aunque los efectos teratogénicos del alcohol son conocidos desde hace años, la prevalencia de los trastornos ocasionados por el consumo del alcohol durante el embarazo sigue siendo alta. El término Trastornos del Espectro Alcohólico Fetal (TEAF, FASD en inglés) engloba las diferentes formas de este trastorno que deja un importante rastro de dificultades cognitivas. Entre los numerosos trastornos que presentan una alta comorbilidad con el TEAF, el Trastorno por Déficit de Atención e Hiperactividad (TDAH) presenta una de las tasas más altas y, pese a años de investigación, la relación entre ambas sigue sin estar clara. Esta revisión trata de resumir la información más actual existente en torno al tratamiento de TEAF/TEAF-TDAH, haciendo hincapié en las diferencias entre ambos trastornos con respecto a las funciones ejecutivas. De hecho, se ha visto que las personas con TEAF no responden igual a la medicación administrada

para mejorar los síntomas de TDAH y que hay poca información acerca de tratamientos no farmacológicos para mejorar las funciones ejecutivas en individuos con TEAF. Los últimos estudios determinan que el entrenamiento cognitivo muestra los mejores resultados, especialmente en combinación con otras terapias como la terapia asistida con animales (TAA), la estimulación transcraneal y la intervención familiar.

Palabras clave: TEAF, TDAH, comorbilidad, tratamiento farmacológico, tratamiento no-farmacológico, funciones ejecutivas.

Laburpena

Alkoholaren eragin teratogenikoak duela urte asko ezagutzen diren arren, haurdunaldian zehar alkohola kontsumitzearen ondorioz sortutako nahasteen prebalentzia altua da oraindik ere. *Fetal Alcohol Spectrum Disorders* (FASD) izenak, aztarna kognitibo nabarmenak uzten dituen nahaste honen aldaera ezberdinak barne-hartzen ditu. FASD-ekin komorbilitate altua duten nahasteen artean, Arreta Gabezia eta Hiperaktibitatearen Nahasteak (AGHN) du tasa altuenetariko bat eta ikerketa-urte askoren ondoren, bien arteko harremana argituta ez egoten jarraitzen du. Errebisio hau FASD/FASD-AGHN-ren tratamenduari buruzko informazio berriena laburbiltzen saiatzen da, funtzio exekutiboei buruzko ezberdintasunak azpimarratuz. Izan ere, FASD duten pertsonek AGHN-rako medikazioaren aurrean modu ezberdinean erantzuten dutela ikusi da eta FASD kasuetan funtzio exekutiboak hobetzeko tratamendu ez-farmakologikoen inguruan informazio gutxi dagoela. Azken ikerketek entrenamendu kognitiboarekin emaitza hoberenak lortzen direla erakusten dute, bereziki animaliekin lagundutako terapia, estimulazio transkraneala edota familia esku-hartzeekin konbinatzerakoan.

Hitz-gakoak: FASD, AGHN, komorbilitatea, tratamendu farmakologikoa, tratamendu ez-farmakologikoa, funtzio exekutiboak.

Introduction

Alcohol consumption during pregnancy can have a damaging impact on the fetus, potentially resulting in various developmental impairments (Abel 1999a; 1999b). These dangerous effects were scientifically described for the first time in 1968 in a study carried out on children of alcoholic mothers (Lemoine, Harousse, Borteyru and Menuet, 1968). In 1973, a similar study was conducted by Jones and Smith, who created the term Fetal Alcohol Syndrome (FAS) to describe a common group of malformations seen in the children of alcoholic mothers. Since then, many studies have been conducted on the effect of prenatal alcohol exposure to child development (Mattson, Bernes and Doyle, 2019).

The physical and neurobehavioural effects of prenatal alcohol exposure are known as Fetal Alcohol Spectrum Disorders (FASD). This term encompasses both the diagnosis of Fetal Alcohol Syndrome (FAS) and other less severe conditions related to prenatal alcohol exposure (Heimdahl, 2020). Among the main characteristics derived from this condition, a broad range of cognitive and behavioural impairments can be found as stemming from neurological changes that affect most areas of the brain. These include overall general intelligence; motor function; attention; activity levels; language development; executive function; visual perception and construction; learning memory; and adaptive functioning. Facial abnormalities and other physical changes may also be found, although not every individual displays these physical features since they only appear in the most severe cases (Mattson et al., 2019).

It is difficult to determine the prevalence of FASD. Differential diagnosis is complicated due to high rates of comorbidity in children with FASD, who tend to be diagnosed with the comorbid disorder instead. Notwithstanding this complication, recent studies estimate the global prevalence of FASD as standing at 7.7 per 1000 of population, with the European region having the highest overall prevalence at 19.8 per 1000 of population. In addition, it has been estimated that 1 out of every 13 babies of mothers who consume alcohol during pregnancy are born with FASD. This would imply that more than 1700 children are born every day with FASD around the world (Lange et al., 2017). Regarding specific regions, the estimated prevalence of FASD in the United States ranges from 1.1% to 5% (May et al., 2018), while the Canadian prevalence is estimated to stand at 1.8% (Popova et al., 2019). When it comes to Spain, although there is very little information on

the prevalence of this spectrum, a recent study estimated the prevalence of alcohol consumption during pregnancy for each trimester as 40.7%, 23.1% and 17.1% respectively (Blasco-Alonso et al., 2015).

As mentioned above, prenatal alcohol exposure tends to have a high comorbidity with other mental health disorders such as attention, anxiety, depression and behavioural disorders (Weyrauch, Schwartz, Hart, Klug, and Burd, 2017). Within this context, FASD seems to be the main cause of Attention Deficit and Hyperactivity Disorder (ADHD) (Burd, 2016). ADHD is the most frequent neuropsychiatric disorder in children where hyperactivity, lack of attention and impulsivity are the main symptoms. A 5% prevalence of ADHD has been estimated in Spain's general population (González Collantes, Rodríguez Sacristán and Sánchez García, 2015). Recent research has shown the inattentive subtype to be the most frequent, followed by the combined and impulsive subtypes, respectively. This disorder requires a clinical diagnosis evidenced by the disruption of the child's functioning in at least two different environments. While genetics are a significant factor in ADHD, different environmental factors can also play a notorious role, especially those that occur during pregnancy and labor (Pelaz and Autet, 2015). Thus, it is no surprise to think of FASD and ADHD as highly related. In fact, higher rates of ADHD have been seen in individuals with FASD, with the latest studies reporting that 50% of individuals diagnosed with FASD have also been diagnosed with ADHD (Mattson et al., 2019; Weyrauch et al., 2017).

Despite this high comorbidity, the mechanisms underlying the link between FASD and ADHD are still unclear and require further research. From the different hypotheses that have been proposed by researchers, two broad tendencies are identifiable. On one side of the field, two hypotheses support the lack of an etiologic link between the disorders. The first of these proposes that the prevalence of ADHD in children is high whether the cause is FASD or not, and so there may be no etiologic relationship between FASD and ADHD. The second hypothesis suggests that although adults with ADHD are more likely to drink alcohol during pregnancy, ADHD is nonetheless inherited through genetic transmission (Oesterheld and Wilson, 1997). On the other side of the field, other hypotheses support the idea of there being a common cause of FASD-ADHD, and ADHD. One of these theories explains the neurochemistry of ADHD as a dysregulation in the frontal-nigrostriatal dopamine system and a dysregulation of the noradrenergic system. Thus, when prenatal alcohol exposure occurs, the teratogen's effect on the development of dopaminergic and

noradrenergic systems results in ADHD. Meanwhile, other studies support the hypothesis that ADHD linked to FASD is actually a subtype of ADHD, but with special characteristics such as an earlier onset, different clinical and neuropsychological features, and likely a different response to medication (O'Malley and Nanson, 2002).

Considering the hypotheses that support a relationship between FASD and ADHD, this review will focus on two of the possible implications of this link. First, regarding responses to medication, it has been found that it is difficult to predict how a person with FASD will respond to psychostimulants, the main drugs used to treat ADHD. This, among other things, implies the importance of the practitioner not solely relying on medicinal treatments, but also on the need to consider other treatment procedures (O'Malley and Nanson, 2002). Second, regarding cognitive implications, various studies have shown a deficit in executive functions in both FASD and ADHD cases, although they seem to be greater in the former. Executive functions include diverse complex cognitive functions which are especially necessary for targeted behaviour (Mattson et al., 2019). Therefore, the aim of this review is to briefly revise the main information available on both treatment response and executive functioning differences in FASD and ADHD.

Topic development

Main pharmacological approach

As referred to earlier, ADHD is one of the most comorbid disorders with FASD, which implies that individuals who have been exposed to alcohol in the uterus usually display inattentive and hyperactive symptoms. Thus, in order to treat these symptoms, clinicians tend to use stimulants, which are the main drugs prescribed for ADHD. The most common substances used for ADHD treatment are dextroamphetamine, methylphenidate and atomoxetine. Studies conducted on the effectiveness of these substances when FASD is involved have generated contradictory results (O'Malley and Nanson, 2002; Mela, 2018).

Some early research on the most efficacious drugs to treat inattentive symptoms indicated that the best results were achieved with dextroamphetamine (O'Malley and Nanson, 2002). Other studies, conversely, showed that methylphenidate was more effective (Doig, McLennan and Gibbard, 2008). More recent research suggests that, for attention deficit, more efficacious results are achieved with dextroamphetamine rather than methylphenidate and that further research is required in order to determine the effectiveness of atomoxetine (Mela et al., 2018). Finally, methylphenidate shows better results when it comes to hyperactive symptoms (Mela et al., 2020).

So, even though using the same medication to treat similar symptoms seems like a reasonable decision, it is clear that when FASD is involved, things are quite different. Indeed, in individuals with both an ADHD and FASD diagnosis, ADHD tends to have an earlier onset while responses to psychostimulants are often worse. More specifically, the reaction of individuals with FASD towards medication is usually unpredictable and drugs can sometimes worsen symptoms (O'Malley and Nanson, 2002). Moreover, non-response to stimulants is generally interpreted as a signal to consider that a diagnosed ADHD case may actually be a FASD-ADHD case instead (Mela et al., 2020).

It is clear that although existing evidence places stimulants as a primary treatment option, when it comes to establishing FASD-ADHD treatment, it is important to remember that firstly, it is a more complicated case than ADHD alone; and secondly, a best practice pharmacological approach has

yet to be identified (Doig et al., 2008), partly due to a lack of information and consensus regarding the link between the two disorders. What is more, the fact that medication for ADHD does not work equally when it is linked to FASD could partially contradict the hypothesis which supports the idea of a common cause for ADHD and FASD-ADHD, since if the neurochemical changes present in ADHD were the same regardless of whether they were caused by alcohol or not, medication should have the same effectiveness in either case. However, seeing that drugs are not always effective, pharmacological intervention should be considered part of a multimodal range of treatment options, alongside other therapies such as behaviour therapy (O'Malley and Nanson, 2002).

Executive functions in FASD and ADHD

Differences between FASD-ADHD and ADHD go beyond pharmacological intervention. Indeed, when it comes to cognitive and adaptive functioning, both groups show different impairment profiles. For instance, significantly greater verbal, perceptual reasoning, working memory, processing speed and adaptive skills deficits are found in children with both FASD and ADHD, compared to those who have ADHD alone (Boseck, Davis, Cassady, Holmes Finch and Gelder, 2015). Closely related to this, impairments in executive functioning have also been reported. Executive functions are said to be some of the most complex processes that human beings can develop and use. Functions such as inhibition, working memory, organisation, planning, problem solving and flexible thinking are among those which help to, for instance, conform the ability to control and organise our actions and cognitions (Flores-Lazaro, Castillo-Preciado and Jiménez-Miramonte, 2014). In essence, one could say that these functions are indispensable for adulthood since they allow for a "normal" life.

Studies have shown that individuals with FASD have greater impairments in respect to their executive functioning when compared to those with ADHD. In particular, weaknesses have been detected in planning, fluency, set shifting and working memory, with more minor deficits reported in response inhibition and attentional vigilance (Kingdon, Cardoso and McGrath, 2016). As for the moderators that could potentially have an influence on executive functions, while the effect of sex is not significant, socioeconomic status and IQ are considered to be significant variables. In fact,

IQ of the FASD group has been proven to aggravate the differences between the two populations. As a result, children with FASD tend to have greater executive functioning deficits and more global cognitive impairment. Nonetheless, no meaningful differences have been found between individuals with FASD and FASD-ADHD, implying that this comorbidity does not exacerbate deficits in executive functioning (Khoury and Milligan, 2019). Given the differences in executive functions between FASD and ADHD groups, the way of approaching each of them is also different.

Non-pharmacological interventions for executive functions

Regarding the differing approaches to FASD and ADHD cases, there is more data available on interventions for the latter. As referred to earlier in this review, diverse studies have tried to elucidate whether a pharmacological or non-pharmacological intervention is best. In this context, it has been seen that non-pharmacological interventions achieve better results in preschool children and in individuals with a mild form of ADHD. However, one cannot deny the efficacy of drugs, which have a major impact on ADHD symptoms, and by extension, on impairments as well (Mela et al., 2018; Mela et al., 2020). Thus, recent studies have determined that a combined usage of pharmacological and non-pharmacological treatments, which effectively complement each other, achieve the best results. While medicines allow for making the most of non-pharmacological therapies, non-pharmacological therapies, in turn, gradually allow for a reduction in necessary drug dose. In any event, the best treatment choice should always be made according to the patient's age, the comorbidities involved and the severity of the disease (Caye, Swanson, Coghill and Rohde, 2019).

In improving specific neuropsychological functions such as executive functions, cognitive training is the most commonly applied technique. Children assist and take part in a range of activities aimed at stimulating different aspects of executive functioning, such as attention, inhibition, memory, hand-eye coordination, balance, sensory awareness, listening skills, and visual focusing, etc. At the same time, metacognitive strategies are applied, as well as behaviour modification techniques such as establishing an environment free of distractions, reinforcing techniques, or time outs (Staff et al., 2021; Tamm, Nakonezny and Hughes, 2014). The results of various studies are contradictory, however. Some suggest that cognitive training demonstrates a mild effect over neuropsychological

functions, achieving better results when activities target more than one executive function rather than when they focus on a single cognitive process (Caye et al., 2019). Meanwhile, others determine that (meta)cognitive training is feasible and effective in improving executive functioning, especially when it comes to visual and auditory attention, ability to follow instructions, working memory and set shifting (Tamm et al., 2014).

As for FASD, there is currently not enough information available. In general, professionals are aware of their lack of knowledge when treating children with FASD and agree that it poses a significant problem. Since most individuals with (or suspected with) FASD also present comorbid diagnoses, intervention is usually approached from the other disorder. In fact, it is commonly believed that treating different aspects of FASD is useful in treating the disorder itself (Bagley, 2018). Considering that ADHD has the highest comorbidity rate with FASD, interventions that have proven to be useful in ADHD cases have been subsequently tried out with FASD. However, although such interventions are appropriate in treating ADHD, they are not always successful among the FASD population. Indeed, there are certain cognitive impairments related to FASD that cannot be improved with medicine, and which, as a result, render the aforementioned interventions ineffective (Bagley, 2018). For example, children with FASD often have reduced brain growth, as well as abnormalities in various essential brain structures such as the frontal lobe and the hippocampus (Boseck et al., 2015). This does not mean to say that there is no way to treat executive functions in FASD. Rather, it simply means that further research is necessary in order to find the best approach. For instance, in a study carried out by Nash et al. (2015), it was observed that training self-regulation improved response inhibition. Furthermore, it was suggested that children tended to perform simple tasks better than complex and multicomponent ones. In fact, the more difficult the task, the more specific strategies are required to perform the task well. These findings could be the basis for future interventions since they help clarify which pathway suits the FASD characteristics best.

Besides behavioural therapy, the effectiveness of other non-pharmacological treatments such as dog-assisted therapy, transcranial stimulation and family interventions has also been studied in individuals with FASD.

Regarding dog-assisted therapy, results indicate that it could help improve other cognitive or behavioural treatments, since the participation of the animal in therapy facilitates the process and can help create a more comfortable environment. This implies that dog-assisted therapy alone does not improve executive functions, but when applied alongside cognitive training, better outcomes would be expected. When it comes to the FASD-ADHD population, improvements have been reported in the areas of social skills and externalising symptoms — reducing severity in the latter (Vidal et al., 2020).

In relation to transcranial direct-current stimulation (a non-invasive way of stimulating the brain with an electrical current), it has been seen that this stimulation can enhance neuroplasticity as well as many cognitive and motor functions of the human brain. Results show a significant improvement in attention span, which is highly relevant in FASD-ADHD cases. By contrast, no significant effect has been reported in respect to working memory. Akin to dog-assisted therapy, and given that the effects of transcranial stimulation are believed to occur along concurrent brain activity, the best outcomes were reported when this form of stimulation was combined with cognitive training (Boroda et al., 2020).

Finally, as parents have the greatest influence over children, it is important to emphasise the significance of family interventions. Researchers have observed how a better comprehension of FASD tends to alter the way misbehavior is treated, usually resulting in better parental skills, which simultaneously improves both parenting self-efficacy and children's externalising behaviour. Regarding executive functioning, studies have shown that the relationship between parents and their children has a significant impact on self-regulation, with children attaining better results in inhibition tasks. Considering how important a good parent-child relationship is in respect to FASD, most studies advocate the necessity of incorporating family-oriented interventions into treatment, which would help parents manage the situation in a more skillful way and result in a better outcome for parents and children alike (Egan, Wilsie, Thompson, Funderburk and Bard, 2020; Petrenko, Demeusy and Alto, 2019; Reid et al, 2017).

Conclusions

The label FASD was created to encompass diverse disorders caused in children after alcohol exposure during pregnancy. Under this umbrella term, there is FAS, the easiest form of FASD to diagnose since physical malformations are present in most cases and neuropsychological consequences are easy to measure. In addition, there are other milder forms which are more difficult to diagnose, as impairments are usually cognitive and easily confused with other disorders that present a high comorbidity with FASD (Heimdahl, 2020; Mattson et al., 2019)

One of the most comorbid disorders is ADHD, characterised by inattention and hyperactivity (Mattson et al., 2019; Weyrauch et al., 2017). On many occasions, children have been diagnosed with this disorder and when treatment has failed to prove useful, the question about what could lie behind the disorder has subsequently arisen — although never beforehand. This shows that the lack of knowledge around disorders provoked by alcohol consumption during pregnancy is widespread. The truth is that there is currently not enough information on these disorders: diagnosis is difficult, stigma and fear of judgment further complicates matters, while many studies cannot be carried out due to ethical concerns and limitations (Bagley, 2018).

Notwithstanding the above, the fact that a significant number of individuals with FASD also have ADHD has made researchers consider what the relation between the two disorders is, and has led to the articulation of several hypotheses arising from this discussion. While some studies state that although FASD and ADHD appear at the same time, there is no common cause, others suggest that the changes produced by alcohol in the fetus' brain are responsible for ADHD. Once again, there is not enough information to reach a clear conclusion on this matter (O'Malley and Nanson, 2002).

This review has sought to summarise the latest information available on FASD-ADHD treatment, focusing on non-pharmacological intervention as a way of improving executive functions, which tend to be highly altered, particularly in individuals with FASD (Kingdon et al., 2016). As for pharmacological intervention, initial attempts to treat inattentive and hyperactive symptoms focused on the main medication that has been proven to be effective in ADHD: stimulants. Nevertheless, different studies have illustrated that these drugs are not always effective in every

FASD case since response is often unpredictable and can even worsen symptoms. This has led some to consider whether the hypothesis of a common cause for both disorders is actually correct, as one would not expect the response to be different in both cases. Due to the little (or non-existent) effectiveness of medicines, it has been proposed that they should be seen as just one component of a broader multimodal intervention, where other treatment options would be carried out at the same time (O'Malley and Nanson, 2002).

Among the range of non-pharmacological treatments, cognitive training is what is mostly used to treat executive functions, although there are varying opinions regarding its effectiveness and the best way to utilise it. Some studies have determined that interventions aimed at improving more than one function at the same time achieve better results, while others have determined that simple tasks, with few components, are more effective. In reality, both results may be supplementary given that, as a result of inattention problems present in most cases, focusing on one activity at a time and ensuring that tasks are simple makes it easier to perform them correctly. Besides, one activity can target multiple executive functions at the same time (Caye et al., 2019; Tamm et al., 2014).

Other treatments such as dog-assisted therapy, transcranial stimulation or family interventions have also proven to be effective, especially when it comes to creating a more suitable environment to apply cognitive training (Boroda et al., 2020; Egan et al., 2020; Petrenko, Demeusy and Alto, 2019; Reid et al, 2017; Vidal et al., 2020). It is through the application of these approaches, combined with cognitive training, that the best outcomes have been obtained, with the importance of family interventions emphasised as a way of creating the right family environment (Egan et al., 2020).

Even though new research conducted on FASD and FASD-ADHD has been published in recent years, information on these disorders remains scarce. With many studies containing only a handful of participants and a high prevalence of inconclusive results, information has been slow to reach health professionals, who often have to deal with FASD cases by putting into practice treatment strategies aimed at specific symptoms. Although positive results are sometimes achieved, treating only certain parts of the disorder is not always effective and caregivers are aware of this fact (Bagley, 2018).

Therefore, and as a final concluding point to this review, it should be stressed that investigating FASD is of significant importance. Only with continued research can the mysteries surrounding this disorder be eventually elucidated. Indeed, psychology plays an important role in this matter, since more clinical research on treatment outcomes should be carried out when children are involved.

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