What we know of the central auditory disorders in children exposed to alcohol during pregnancy? Systematic review

O que sabemos das alterações auditivas centrais em crianças expostas ao álcool na gestação? Revisão sistemática

ABSTRACT

Purpose: To identify the effects of alcohol intake during pregnancy on the central auditory nervous system in relation to their possible diagnosis, Fetal Alcohol Syndrome, partial Fetal Alcohol Syndrome, Alcohol-Related Birth Defects and Alcohol-Related Neurodevelopmental Disorder, his extension and the hearing assessment method. Research strategy: Systematic and integrative review searched the databases PubMed, LILACS and SciELO, with terms in Portuguese and English “fetal alcohol syndrome”, “alcohol-related disorders” associated with “hearing”. Selection criteria: We identified 123 abstracts, six were selected and published until May 2015. Data analysis: Were listed topics to be answered, characterization of the sample; the diagnosis result of fetal exposure; method of hearing assessment and described results. Results: Among the behavioral assessments, Verbal Dichotic Tests with syllables and sentences and Speech in Noise Test, were used. Among the electrophysiological tests, the Brainstem Auditory Evoked Potential was detected change neural synchrony, and Long-Latency Auditory Evoked Potential – P300, early latency values. Conclusion: There is evidence that children exposed to alcohol in utero present central auditory nervous system involvement signals, but it was not possible to identify the influence of different subtypes and their losses. Cortical auditory pathways were the most investigated and the electrophysiological method as used with an unexpected result in two of them, early N2 and P300 latency.

RESUMO

Objetivo: Identificar os efeitos da ingestão de álcool na gestação sobre o sistema nervoso auditivo central em relação aos seus possíveis diagnósticos, Síndrome Fetal do Álcool, Síndrome Fetal do Álcool Parcial, Distúrbios ao Nascimento Relacionados ao Álcool e Distúrbio do Neurodesenvolvimento Relacionado ao Álcool, sua extensão e o método de avaliação auditiva. Estratégia de pesquisa: Busca sistemática e integrativa nas bases de dados PubMed, LILACS e SciELO, com os termos em português e inglês “síndrome fetal do álcool”, “desordens relacionadas ao uso do álcool” associadas a “audição”. Critérios de seleção: Dos 123 resumos identificados, foram seis selecionados, publicados até maio de 2015. Análise dos dados: Foram elencados tópicos a serem respondidos, caracterização da casuística; o diagnóstico decorrente da exposição fetal nas crianças; método de avaliação auditiva; e resultados descritos. Resultados: Entre as avaliações comportamentais, foram utilizados os testes dicóticos verbais com sílabas e com palavras e o teste fala com ruído. Entre os testes eletrofisiológicos, no Potencial Evocado Auditivo de Tronco Encefálico, foi detectada alteração de sincronia neural, e no Potencial Evocado Auditivo de Longa Latência – P300, valores de latência precoce. Conclusão: Existem evidências de que as crianças e adultos jovens expostos ao álcool na gestação apresentam sinais de comprometimento do sistema nervoso auditivo central, mas não foi possível caracterizar essas alterações nos diferentes subtipos diagnósticos do espectro. As vias auditivas corticais foram as mais investigadas e o método eletrofisiológico o mais utilizado, com um resultado inesperado em dois deles, a latência precoce da N2 e da P300.
INTRODUCTION

The diagnosis of the effects of alcohol intake during pregnancy at birth or during child development is still a challenge\(^1,\text{2}\). The events described by Jones and Smith in the early 1970s\(^3\) included changes in pre- and/or post-natal development such as facial dysmorphism (undefined philtrum, palpebral fissures, thin upper lip, flattened face) and dysfunction of the central nervous system (CNS) (intellectual disabilities and/or attention deficit). The aforementioned authors\(^3\) named this set of signs Fetal Alcohol Syndrome (FAS), and some of these events had been described earlier by Lemoine et al\(^4\).

With the documentation of new cases of FAS, it was observed that the signs initially described were not always present all together and, when they were present, severity levels varied, thus the term Fetal Alcohol Spectrum Disorder (FASD) was proposed\(^5\). Manifestations of this condition include neurological abnormalities characterized by behavioral disorders, neuropsychomotor development delay, intellectual impairment, and sensory and perceptual changes\(^6\text{—}9\). There are other labels under the umbrella term FASD owing to the heterogeneity of manifestations: Partial Fetal Alcohol Syndrome (pFAS), Alcohol-Related Birth Defects (ARBD), and Alcohol-Related Neurodevelopmental Disorder (ARND)\(^1\). Therefore, it is possible to infer that the impact of FAS/FASD on child development results from the extension and severity of manifestations which, in turn, can be related to the dose and time of maternal exposure to the drug\(^\text{10}\).

Sensory damages described in the population with FAS/FASD include conductive and sensorineural hearing losses, which occur in 70% - 77% and 29% of cases, respectively\(^11\text{—}14\). The significant presence of conductive hearing loss may be associated with the occurrence, in the same population, of craniofacial deformities, including cleft palate\(^15\), which are known etiologies for this type of loss\(^16\).

Central auditory nervous system (CANS) impairment in FAS was first described in the 1990s by means of auditory, behavioral and electrophysiological assessments\(^12\). Altered results were found in 15% of children in the Brainstem Auditory Evoked Potential (BAEP) and in 100% of children in behavioral assessments such as Verbal Dichotic Tests.

The occurrence of an abnormal neurophysiological representation of the sound stimulus in the CANS is named Auditory Processing Disorder (APD)\(^17\). Currently, it is recommended that its diagnostic evaluation be conducted through a set of electrophysiological and behavioral tests, with verbal and nonverbal stimuli\(^17\). These recommendations are supported by a better understanding of the neural mechanisms involved in behavioral and electrophysiological tests, including component P300 and Mismatch Negativity (MMN).

Considering the variability of FAS/FASD manifestations and their severity, the diagnostic assessment of auditory potentials can be useful because it describes the origin and extension of the APD, and this characterization is essential to the management of an individual therapeutic intervention program.

OBJECTIVE

In view of the harmful impact of FAS/FASD on child development, the present literature review aims to identify the effects of alcohol intake during pregnancy on the CANS in relation to the possible different diagnoses of the condition, the hearing assessment method, and event-related characterization.

RESEARCH STRATEGY

A systematic, integrative search was conducted at the PubMed, LILACS, and SciELO databases using the following terms in Portuguese: “síndrome fetal do álcool”, “desordens relacionadas ao uso do álcool”, “audição”; and in English: “fetal alcohol syndrome”, “alcohol-related disorders” associated with “hearing”.

SELECTION CRITERIA

In the first phase, the following criteria were established for the reading of abstracts: inclusion: a) studies in humans, b) children, adolescents, and young adults with a history of fetal alcohol exposure, c) studies without a time limit published until May 31, 2015, d) available abstract, e) citation of hearing assessment in the same abstract, and f) publication in English, Portuguese, or Spanish; exclusion: a) literature reviews, b) letters and editorials, and c) case reports. In the second phase, the following new exclusion criteria were established for the reading in full of the selected works: absence of one of the possible diagnoses for fetal alcohol exposure (FASD, FAS, pFAS, ARBD, ARND) and absence of description of the hearing assessment procedure.

DATA ANALYSIS

The selected papers were analyzed by two speech-language pathologists. After analysis, they filled in a spreadsheet with the following information: a) author and year; b) type of study and level of evidence; c) sample description; d) diagnosis of fetal alcohol exposure; e) description of the auditory function assessment method and its classification: behavioral vs. electrophysiological; f) hearing assessment outcomes; and g), in the presence of abnormal results, impairment extension: subcortical vs. cortical. To underpin the interpretation regarding the methodological design of each of the articles, a classification criterion of evidence levels, from 1 to 5, was adopted according to the Oxford Centre for Evidence-based Medicine – Levels of Evidence (March 2009)\(^18\). Subsequently, to identify the possible generalization of the results found, each text was also rated according to grade of recommendation\(^19\). The spreadsheets of both speech-language pathologists were then compared. In the presence of divergence in any of the items, the article...
was read in full by both examiners. If disagreement persisted, a third health professional was consulted.

RESULTS

Based on the selected search terms, 130 titles were identified, from those 123 abstracts were found. After reading and application of the inclusion and exclusion criteria, 35 articles, 26.9% (35/130) of the total, were selected. Upon reading the abstracts, the examiners found that 27 (79%) articles did not present a description of the diagnosis of the individual exposed to alcohol during pregnancy, only a reference to it, and that two (0.5%) articles used auditory cognitive assessment subtests for the outcome of the auditory processing disorder; therefore, these 29 articles were excluded from the study.

Figure 1 shows a flowchart of the search conducted at the scientific databases.

Eventually, six articles were identified and summarized according to the survey questions (Chart 1).

FAS/FASD AND ITS SUBTYPES AND LEVELS OF EVIDENCE

The six selected studies addressed the diagnostics of individuals exposed to alcohol during pregnancy, four of them exclusively on FAS, one of them on FAS and pFAS, and one on FAS, pFAS and ARND. Of the four studies that addressed diagnostics exclusively on FAS, three were from the 1990s, and the two studies that used the sub-labels of the FAS/FASD were published in the year or after the guiding publications, with guidelines on the theme.

All six papers used a sample of individuals with partial or complete FAS, which represent a profile of greater clinical severity within FASD. Although children with the complete syndrome are associated with profiles of higher alcohol consumption during pregnancy, the respective articles did not report information on the characteristics of alcohol use by the mother.

All selected studies were conducted using the cross-sectional design. None of them presented longitudinal and/or cohort characteristics, but four of them used control groups for comparison with the study groups. The cross-sectional study with a control group shows level of evidence “3” and grade of recommendation “B”. The other two papers show level of evidence “4” and grade of recommendation “C”. It is worth mentioning that 66.6% (4/6) of the articles, those with grade of recommendation “B”, presented credible outcomes, that is, their results can be generalized for the studied conditions and should be used for clinical decision making. The studies with grade of recommendation “C” suggest that conditions may be clinically different from those used in the study.

Caption: FAS = Fetal Alcohol Syndrome; pFAS = Partial Fetal Alcohol Syndrome; ARND = Alcohol-Related Neurodevelopmental Disorder; FASD = Fetal Alcohol Spectrum Disorder

Figure 1. Flowchart of the selection process of the articles
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study design</th>
<th>Sample</th>
<th>Diagnostics</th>
<th>Levels of evidence and grades of recommendation*</th>
<th>Diagnostic evaluation: behavioral vs. electrophysiological vs. electroacoustic</th>
<th>Subcortical vs. cortical</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stephen et al.</td>
<td>Cross-sectional - Case control</td>
<td>10 children exposed to alcohol 15 control children Age: 3 - 6 years</td>
<td>FASD (FAS, pFAS, ARND)</td>
<td>Level of evidence: 3b Grade of recommendation: B</td>
<td>Electromagnetic technique with Oddball paradigm</td>
<td>Cortical</td>
<td>Increased latency between the groups.</td>
</tr>
<tr>
<td>Steinmann et al.</td>
<td>Cross-sectional - Case control</td>
<td>24 children exposed to alcohol 20 control children Age: 11 - 15 years</td>
<td>FAS and pFAS</td>
<td>Level of evidence: 3b Grade of recommendation: B</td>
<td>Electrophysiological with Oddball paradigm Complex P2-N2-P3</td>
<td>Cortical</td>
<td>N2 with greater latency in frequent stimulus in the study group Frequent vs. rare stimuli; the study group presented earlier N2 in the rare stimulus; this outcome was not observed in the control group.</td>
</tr>
<tr>
<td>Damelöf et al.</td>
<td>Cross-sectional - Case control</td>
<td>11 children exposed to alcohol 14 control children Age: 8 - 17 years</td>
<td>FAS</td>
<td>Level of evidence: 3b Grade of recommendation: B</td>
<td>Behavioral Verbal dichotic test</td>
<td>Cortical</td>
<td>Children with FAS presented right ear advantage less frequently (considering the pairing of hand dominance).</td>
</tr>
<tr>
<td>Church et al.</td>
<td>Cross-sectional</td>
<td>22 children exposed to alcohol Age: 3 - 26 years</td>
<td>FAS</td>
<td>Level of evidence: 4 Grade of recommendation: C</td>
<td>Electrophysiological and behavioral BAEP Test of everyday attention and speech-in-noise test</td>
<td>Subcortical and Cortical</td>
<td>15% of the 22 assessed individuals presented altered BAEP outcomes. 100% of the 12 individuals who underwent behavioral assessment presented altered outcomes.</td>
</tr>
<tr>
<td>Kaneko et al.</td>
<td>Cross-sectional - Case control</td>
<td>18 children exposed to alcohol 18 children with Down Syndrome 18 control children Age: 8 years (mean)</td>
<td>FAS</td>
<td>Level of evidence: 3b Grade of recommendation: B</td>
<td>Electrophysiological N1 and P3</td>
<td>Cortical</td>
<td>The P300 with lowest values of amplitude and latency in the study group with the active electrode in the active electrode in the frontal region.</td>
</tr>
<tr>
<td>Rössig et al.</td>
<td>Cross-sectional</td>
<td>36 children exposed to alcohol</td>
<td>FAS</td>
<td>Level of evidence: 4 Grade of recommendation: C</td>
<td>Electrophysiological BAEP</td>
<td>Subcortical</td>
<td>21% with altered outcomes due to the changes in the neural structures of the auditory pathway. More frequent alteration, greater latency of the V wave, or even absence, and increased latency of the III wave.</td>
</tr>
</tbody>
</table>

*Oxford Centre for Evidence-based Medicine – Levels of Evidence (March 2009)*

**Caption:** FASD = Fetal Alcohol Spectrum Disorder; FAS = Fetal Alcohol Syndrome; pFAS = Partial Fetal Alcohol Syndrome; ARND = Alcohol-Related Neurodevelopmental Disorder; CG = control group; BAEP = brainstem auditory evoked potential; P3/P300 = third positive peak of the cortical auditory evoked potential; P2 = second positive peak of the cortical auditory evoked potential; N2 = second negative peak of the cortical auditory evoked potential. Levels of evidence: 1A = systematic reviews of randomized controlled trials; 1B = individual randomized controlled trials; 1C = “all or none”; 2A = systematic reviews of cohort studies; 2B = individual cohort studies including low-quality randomized controlled trials; 2C = “outcomes” research, therapeutic or ecological studies; 3A = systematic reviews of case-control studies; 3B = individual case-control studies; 4 = case series including cohort studies; 5 = based expert opinions. Grades of recommendation: A = consistent level 1 studies; B = consistent level 2 or 3 studies or extrapolations from level 1 studies; C = level 4 studies or extrapolations from level 2 or 3 studies; D = level 5 evidence or troublingly inconsistent or inconclusive studies of any level.
EVALUATION OF CENTRAL AUDITORY PATHWAYS

Only one study\(^1\) used both behavioral and electrophysiological techniques on the hearing assessment. For the other selected works, one article\(^2\) used behavioral evaluation and three papers\(^3,4,5\) applied electrophysiological measurement. There was another only study\(^6\) in which the authors chose magnetoencephalography (MEG) with Oddball paradigm to investigate the cortical activation of auditory stimuli.

The following behavioral assessments were used: verbal dichotic listening test (VDT) with syllables\(^7\), competing sentence test (CST) in contralateral mode, and speech-in-noise test (SNT)\(^8\). Verbal dichotic listening tests are commonly associated with cortical auditory disorders, whereas the SNT is susceptible to both cortical and subcortical disorders\(^9,10\); nevertheless, there are signs that noise attenuation begins at the superior olivary complex\(^11\). VDT\(^12\) was employed to investigate the right ear advantage (REA), a sign commonly present in right-handed individuals\(^13\) that reflects the dominance of the left hemisphere for linguistic sounds. The authors\(^14\) reported that REA occurred less frequently compared with the control group pairing the number of right-handed individuals in both groups. Changes in the outcomes of CST and SNT\(^15\) were found in 100% of the individuals assessed (n=12), with an initial sample of 22 individuals; the authors reported that only 12 of the 22 study participants attended the behavioral hearing assessment, with no further specifications.

Four of the six selected articles used auditory evoked potentials\(^16,17,18,19\). Brainstem Auditory Evoked Potential (BAEP) was chosen in two studies\(^16,17\), both addressed the diagnosis of FAS, with the outcomes suggesting that alteration in neural synchrony was similar between them, 21%\(^18\) and 15%\(^19\). The two studies also described increasing interpeak latencies involving waves III and V as a suggestive sign of abnormality, that is, dysfunction involving the superior olivary complex and lateral lemniscus/inferior colliculus\(^20\).

The other two studies used the recording of late or long latency potentials\(^21,22\); the first survey\(^21\) analyzed components N1 and P300 and observed that children with FAS presented smaller amplitude and latency at P300 compared with those of the control group with the active electrode in the frontal position; whereas the latter article\(^22\) used the recording of components P2, N2 and P300 and observed that the children exposed to alcohol during pregnancy presented greater latency at N2 in the recording of the frequent stimulus compared with those of the control group. They also compared the variables in each group with respect to the frequent and rare stimuli and verified that component N2 presented difference in the latencies, with early latency in the rare stimulus - a result not observed for the control group.

The sites generated by the long-latency auditory evoked potentials (LLAEP) are not accurate; however, it has been accepted that component P2 have its origin, not only but also, in the thalamic region, with extensions of the limbic and reticular systems\(^23,24\). P300 is considered an endogenous component dependent on the attentional process, considering that it demands a mental or motor task for a given sound stimulus, called rare. Its multiple generators are located in the thalamus, hippocampus, and frontal cortex\(^25,26\).

Only one study associated the different types and diagnoses of fetal alcohol exposure with the assessment outcome\(^27\). The authors recorded the sound stimuli by means of magnetoencephalography (MEG) with Oddball paradigm and observed that children exposed to alcohol during pregnancy presented increased latency compared with those of the control group, but the subtypes of the spectrum (FAS, pFAS and ARND) were not included in the analysis. Increased latency was identified in components M1 and M2, which correspond to the superior temporal gyrus area.

An important aspect for consideration of the hearing assessment of CANS is that, in addition to intrauterine exposure to alcohol, there are other known risk factors for its dysfunction\(^28\). These factors include, but are not limited to, hyperbilirubinemia with levels for exchange transfusion, Apgar score, and bacterial or viral infections. Although the selected articles report the occurrence of other risk factors for these types of alterations, they did not identify them, and did not mention the possibility of risk factor overlapping\(^15,21,28\).

CONCLUSION

Children and young adults exposed to alcohol in utero present central auditory nervous system (CANS) impairment signs, but no influence of the different FAS/FASD subtypes on these losses was identified. The cortical auditory pathways were the most investigated and the electrophysiological assessment was the most used method, with unexpected results for early N2 and P300 latencies. Only one study associated behavioral and electrophysiological techniques on the hearing assessment.

REFERENCES

Central auditory pathways and alcohol exposure


Author contributions
HOS participated in the design and schedule of the study, literature review, analysis and critical interpretation of data, and writing of the manuscript; SZ was the study co-advisor; participated in the design and schedule of the study, literature survey, analysis and critical interpretation of data, writing of the manuscript; and approval of its final version; EFF was the study advisor, participated in the design and schedule of the study, literature survey, analysis and critical interpretation of data, writing of the manuscript; and approval of its final version.