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Italian Guidelines for the diagnosis and treatment of Fetal Alcohol Spectrum Disorders: cognitive and behavioral deficits

GIOVANNA CORIALE[1], ARIANNA BARZACCHI[2], MAURO CECCANTI[2], LUIGI TARANI[3], SIMONA GENCARELLI[1], MARIA GIUSEPPA ELMO[4], MARTINO MISTRETTA[1], MARISA PATRIZIA MESSINA[3], SIMONE DE PERSIS[5], MARCO FIORE[6], DANIELA FIORENTINO[7]; INTERDISCIPLINARY STUDY GROUPS* SAPIENZA, AIDEFAD, SITAC, SIFASD, FIMMG-LAZIO, SIPPS, SIMPESV, CIPE

[1]CRARL Lazio, ASL Roma 1, Italy; [2]SITAC - Società Italiana per il Trattamento dell'Alcolismo e le sue Complicanze, Rome, Italy; [3]Department of Maternal Infantile and Urological Sciences, Sapienza University of Rome, Italy; [4]Department of Mental Health, ASL Roma 1, Italy; [5]Department of Mental Health, Rieti, Italy; [6]Institute of Biochemistry and Cell Biology (IBBC-CNR), Department of Sensory Organs, Sapienza University of Rome, Italy; [7]ASL Rieti, Italy.

Summary. Objective. Fetal alcohol spectrum disorders (FASDs) refer to a group of clinical conditions that occur in a person exposed to alcohol before birth. Neuroimaging shows abnormalities in brain structure, cortical development, white matter microstructure, and functional connectivity in individuals with FASD. These abnormalities modify the normal developmental trajectories resulting in deficits in cognition and behavior across several domains, including general intelligence, memory, language, attention, learning, visuospatial abilities, executive functioning, fine and gross motor skills, and social and adaptive functioning. This paper provides a review of the cognitive and behavioral outcomes of prenatal alcohol exposure. Updates data on FASD-specific neurobehavioral profile and its potential as a diagnostic tool will then be presented.

Key words. ARND, behavior problems, cognitive development, FASD, neurobehavioral profile.

Linee guida italiane per la diagnosi e il trattamento dei disturbi dello spettro feto-alcolico: deficit cognitivi e comportamentali.

Sommario. Obiettivo I disturbi dello spettro feto-alcolico (FASD) fanno riferimento a un gruppo di condizioni cliniche causate dall'esposizione all'alcol durante la gravidanza. Gli studi di neuroimmagini stanno fornendo evidenze sulla presenza di anomalie nella struttura cerebrale, nello sviluppo corticale, nella microstruttura della materia bianca e nella connettività funzionale nei soggetti con FASD. Queste anomalie modificano le normali traiettorie di sviluppo, con conseguenti deficit che influenzano molteplici aspetti della cognizione e del comportamento in diversi domini, tra cui l'intelligenza generale, la memoria, il linguaggio, l'attenzione, l'apprendimento, le abilità visuo-spaziali, il funzionamento esecutivo, le abilità motorie fini e grossolane e il funzionamento sociale e adattivo. Questo documento fornisce una revisione degli esiti cognitivi e comportamentali dell'esposizione prenatale all'alcol. Verranno poi presentati i dati aggiornati sul profilo neurocomportamentale specifico della FASD e il suo potenziale come strumento diagnostico.

Parole chiave. ARND, FASD, problemi comportamentali, profilo neurocomportamentale, sviluppo cognitivo.

Introduction

Fetal alcohol spectrum disorders (FASD) refer to a broad spectrum of physical, mental, behavioral, and cognitive abnormalities occurring in individuals with a history of prenatal alcohol exposure (PAE) by the mother or the father[1-3] including fetal alcohol syndrome (FAS), partial FAS, alcohol-related neurodevelopmental disorder (ARND) and alcohol-related birth defects (ARBDs)[4]. FASD is associated with several neurobehavioral impairments including general intelligence, adaptive function, attention and executive function, motor function, social cognition, visual-spatial functioning, verbal and nonverbal learning as well as internalizing and externalizing behaviors[5]. Morton and Frith's model can be used to describe FASD-related neurocognitive and behavioral disorders according to three levels of analysis: neurobiological, cognitive, and behavioral[6].

Neurobiology: structural and functional alterations

A baby with FASD may be born with a head and brain significantly smaller than a normal-sized baby of the same gender and age. Concerning FASD, microcephaly reflects structural damage to the brain. Studies of brain structure using neuroimaging techniques have shown the global and focal effects that prenatal alcohol exposure has on the brain demonstrating reductions in the volume of various brain structures, including total brain, corpus callosum, cerebellum, and basal ganglia[7,8]. Alterations in the corpus callosum, often damaged by PAE, have been associated with deficits in several domains of neuropsychological function such as motor function[9], attention[10], verbal learning[11], and executive function[12]. Notably, the caudate was the first reported region to have a lower volume associated with prenatal alcohol exposure[13], a finding that has been consistently reported in the literature[14-16]. In addition, the volume of the parietal, temporal, and frontal lobes have all shown locally decreased volume in FASD children and adolescents relative to controls[14,17]. Very interesting the results of several studies that used task-based fMRI designs have examined the brain function of subjects while performing a cognitive task. Altered brain function has been observed in FASD during various cognitive tasks, including response inhibition, mathematics, and number processing, working memory and verbal learning[18] showing more regional functional demand in children/adolescents with FASD.

According to well-documented structural and microstructural abnormalities in PAE, recent studies suggest that also functional connectivity (FC) may be altered in individuals with FASD[19]. In FASD, alterations have been found both within and between most cognition-related networks[20,21].

Cognitive impairments

Cognitive deficits affect different domains of cognition[5,22-27]. The domains are closely related to each other so the alteration of one affects all the others and are hierarchical, with the bottom referring to more basic sensory and perceptual processes and the top referring to elements of executive functioning and cognitive control[28]. The executive tasks often involve coordinating multiple sensory, perceptual, attentional, and other less complex functions, while simple sensory tasks demand minimal higher-level processing. The top-down vs bottom-up perspective will be used to describe cognitive impairment in FASD.

Sensation and perception

The sensory information is processed and integrated into the domain of perception. One of the important goals of perception is the identification of previously experienced objects from sensory information and can be assessed in terms of the ability to recognize objects, sounds, and perceptual field in its entirety. It has been found that children with FASDs have a high prevalence of ophthalmologic abnormalities, as subnormal visual acuity (VA), optic nerve hypoplasia (ONH), retinal vascular malformations; refractive errors, and strabismus are well documented in FASDs[29,30].

Thus, an ophthalmological assessment should be an integral part of the FASD diagnostic workup, to better understand the nature of sensory and perceptive problems if they were present[31]. Sensory processing (also called sensory integration) refers to the way the individual's nervous system receives signals from sensory modalities and transforms them into motor and behavioral responses while the ability to identify a meaningful stimulus falls under the domain of perception[32]. Sensory Procession Disorder (SPD) leads to inappropriate behavioral reactions to environmental stimuli making it difficult to organize sensory signals into appropriate responses[33] and since it is commonly comorbid with FASDs, early recognition, diagnosis, and referral for SPDs is important when diagnosing FASD. The occurrence of visual perception problems (VPPs) in children with FASD has previously been reported and their persistence into adulthood has not yet been investigated[29]. Deficits related to FASD have been described in visual perception[34], visual construction[35], and feature processing[36] (figure 1).

Motor skills and visuospatial construction

Motor skills refer to fine motor abilities, including manual dexterity and motor speed, as well as reaction time, and gross motor skills such as balance. The prevalence of serious fine and gross motor deficits among children diagnosed with FASD is estimated at 51% and 37%, respectively, with clinically important developmental delays more in fine motor skills than in gross motor skills[37]. Severe fine motor impairment can adversely affect the child's ability to meet daily activity demands, making those difficult to operate and not supporting independence in self-care tasks such as dressing, eating, brushing hair, and cleaning teeth; academic skills including handwriting, drawing, and using scissors; and participation in play and social activities[37]. Visual-motor integration (VMI) can be defined as the extent to which visual perception and finger-hand movements are well coordinated. Testing in this domain examines the accuracy of an individual's perception of stimuli and their related ability to appropriately manipulate objects in the environment[38]. Studies have found that VMI skills have a positive influence on fine motor development, handwriting performance, and academic achievements[39]. Children with FASD have been found poor in VMI and fine motor coordination skills[40-44].

The capacity to see an object or image as a composite of parts and then to construct the original from these parts is referred to as visuospatial constructive cognition[45]. Children with FASD seem to have difficulty seeing the complex object as a whole or 'gestalt,' and integrating pieces of the design into a cohesive whole[46]. Deficits include problems with basic figure copying, spatial learning, spatial working memory,

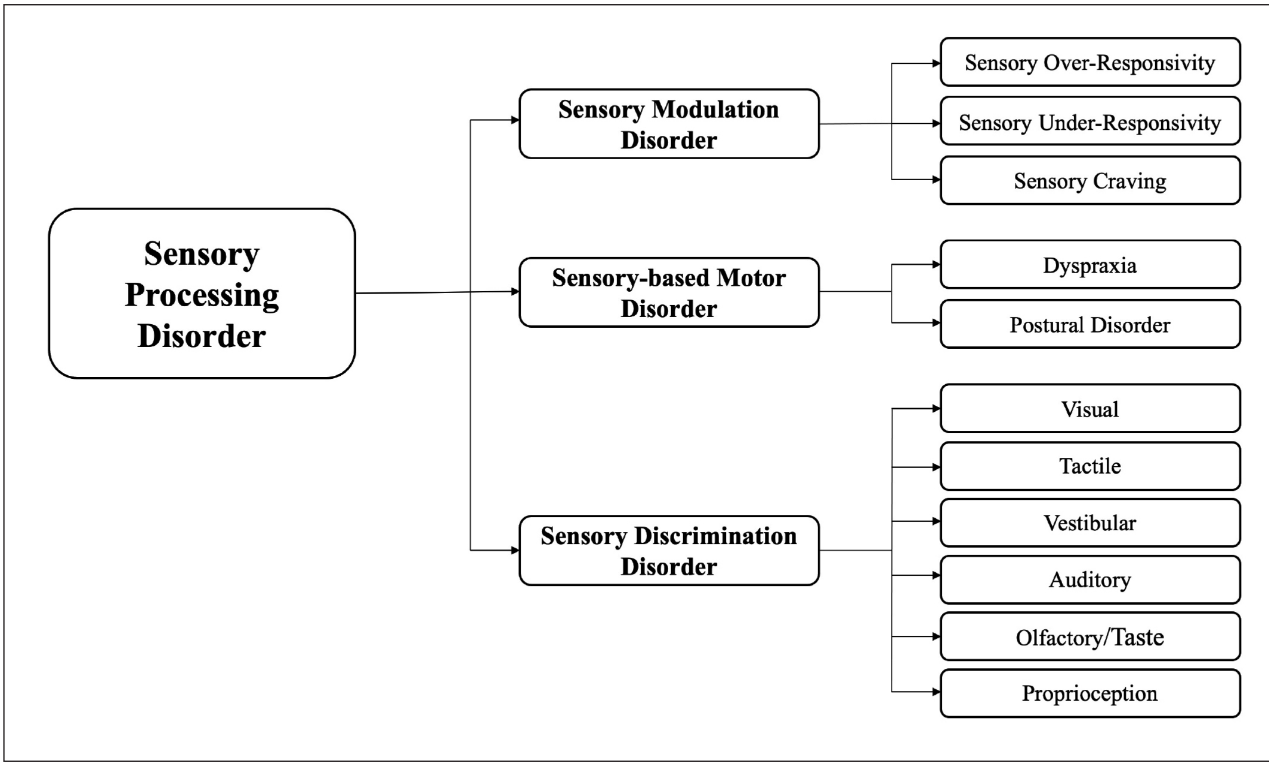

Figure 1. The three primary sensory processing disorders descriptions.

spatial recall, visual-spatial reasoning, visual-perceptual matching (e.g., matching complex geometric shapes), and sustained visual attention[23,47,48]. Since early motor skill, VMI and visuospatial deficits have been found to have an important and negative impact on functional abilities and academic achievement, physiotherapists and occupational therapists should support the diagnosis of FASD by conducting assessments of the motor domain and providing strategies[49,50].

Memory and learning

Memory is an important cognitive function that allows us to acquire, retain, and recover data. Three main processes that characterize how memory works are encoding, storage, and retrieval (or recall). Memory isn't a single unitary phenomenon and is composed of several distinct but interrelated constituent processes and systems[51]. There are three major types of human memory: working memory, declarative memory (explicit), and non-declarative memory (implicit). Working memory is a limited capacity store for retaining information for a brief period while performing mental operations on that information. It is critical for a variety of activities at school, from complex subjects such as reading comprehension to mental arithmetic[51]. Clinical studies have reported learning and memory deficits in children with heavy PAE. These impairments range across specific aspects of learning and memory, including verbal and nonverbal skills[52-54]. Surprisingly, memory impairment in individuals with FASD has been found the result of erroneous encoding processes rather than retrieval impairments[5,55-57]. Researchers have obtained evidence of working memory deficits in children with FASD[26,58]. Impairments in spatial working memory are also evident, with deficits becoming more significant as the task increases in complexity[59].

Language

Language skills include receptive (comprehension) and productive (speech) abilities as well as the ability to access semantic memory, to identify objects with a name, and to respond to verbal instructions with behavioral acts[28]. Language skills are assessed with measures of fluency by asking to name as many animals as possible, object naming and responding to instructions. Evidence from the longitudinal studies suggests that PAE causes delays in receptive and expressive communication[60]. Various language impairments have been described including problems in speech discrimination, comprehension, syntax development, and prosodic features. However, a child with FASD may present adequate superficial speech skills but also an impairment in pragmatic language use, resulting in poor peer relationships and thus significant social problems[61]. Preschool children with fetal alcohol exposure have been reported as having social communication deficits and adverse social interactive experiences[14].

Attention

Over the years, researchers have identified various types of attention in psychology. Selective attention is the process of attending to information that is relevant and important and ignoring other non-relevant information. Selective attention tasks often provide distracting information and request the examinee to attend specifically to the relevant information. Instead, sustained attention is the ability to sustain attention over time. Tasks measuring sustained attention as continuous performance tasks often require the detection of simple stimuli presented infrequently during a stream of other stimuli[62].

When the focus is on two or more things at the same time, divided attention is used. This ability is also known as multitasking and is a crucial factor in the academic setting. The Stroop test is one of the most important tests used to measure divided attention[63,64]. These studies support the idea that there is a behavioral impairment in the ability to maintain focused alertness in perceiving a signal and in the ability to allocate attentional resources, or the ability to shift attention from one task to another when appropriate[65,66]. Additionally, attending to visual information appears to be more severely impaired compared to auditory information[10,67]. Coles et al.[68] found a greater difficulty in Encode (i.e., the capacity to hold information temporarily in memory while performing a mental operation upon it) and Shift (e.g., the ability to shift attention from one stimulus dimension to another in a flexible manner) components in FASD group. In contrast, the ADHD group displayed greater difficulty on tests assessing Focus (i.e., the capacity to concentrate on a particular task) and Sustain (i.e., the ability to stay on a task) components.

Executive functioning and information processing

Executive functions (EFs) are a set of cognitive skills that are needed for self-control and managing behaviors. These skills include high-order cognitive abilities such as working memory, inhibitory control, cognitive flexibility, planning, reasoning, and problem-solving allowing people to follow directions, focus, control emotions, and attain goals[69]. The executive system manages and controls other cognitive abilities (for example attention and memory) and allows individuals to change their overlearned behavioral patterns when they become unsatisfactory[70]. This makes also possible to adapt to new and complex daily life situations[66]. Consequently, deficits in EFs have important impacts on everyday life, which include poor goal-directed behavior and impaired social functioning[71]. Traditionally those have been associated with frontal lobe functioning, but posterior and subcortical regions also play a crucial role in EF processing, especially in the integration of sensory information and emotion. Frontal circuits are particularly vulnerable to PAE as shown by fMRI studies examining executive functioning[72]. The disruption in executive functioning is one of the most important distinctive signs of FASD, characterized by problems with self-control and self-regulation[59,73-75]. Weaknesses are most consistent for measures of planning, fluency, and set-shifting[76]. EF deficits have been found evident before the age of 6 years in children with FASD, present across all the spectrum and impaired in children with more severe forms of FASD and/or lower IQs and are related to difficulties in daily functioning in children with FASD, limiting independence (routine activities like getting dressed require sequencing skills) and disrupting social interactions[77,78]. Executive Functioning has been categorized into two domains, cognition-based EF, and emotion-related EF. The original concept of EF referred to cognition-based actions, and researchers and clinicians have used a variety of cognitive tests requiring deliberate attention to formally assess this type of EF. Such tests measure problem-solving, conceptual set-shifting, and rapid generation of verbal or nonverbal responses. Another form of action selection has been called emotion-related[79]. Action selection at this level is based on rewards and punishments (positive and negative reinforcements) obtained in the past in similar situations. This emotion-related EF can be assessed using tests that measure the ability to modify behavior in response to changing reinforcement conditions[80]. Anyway, FASD shows impairments for both domains, having them appear to be good predictors of behavioral problems in alcohol-affected people[81-84]. Therefore, identifying and treating EF deficits overall years earlier may consistently help reduce the severity of problems including disruptive behavior and learning deficits[85,86].

In addition, a large body of neuropsychological research on children with FASD highlights a pattern where affected children succeed at simple tasks but display greater difficulty on more complex tasks[87]. This illustrates how PAE disrupts the processing and integration of complex information, especially when they are required to hold and manipulate information in working memory[87].

General intelligence

One of the first neurocognitive findings related to exposure to alcohol during pregnancy has been diminished intellectual capacity[52]. FASD is known as a preventable cause of intellectual disability[88]. Intelligence is a general mental ability for reasoning, planning, solving problems, thinking abstractly, comprehending complexity, and learning. Most studies that assessed the overall intelligence of individuals prenatally exposed to alcohol have used the Wechsler Intelligence Scales. It includes the WAIS, the WISC, and the WPPSI (Wechsler Preschool and Primary Scale of Intelligence) and is used for the assessment of intellectual ability across the lifespan[89]. Fortunately, only a minority of individuals with FASD are intellectually disabled (defined as overall IQ score <70 and adaptive disability), while the majority have borderline cognitive functioning[90]. As for the factorial indexes of the Wechsler Scales, the Working and Memory Index was the most adversely affected, with loss of attention, concentration, immediate memory, and mathematical skills. As for the Wechsler Scales subtests, there have been found more severe deficits in the arithmetic[91]. In a very recent study, a generally low performance of children with FASD was confirmed on all subtests of WISC, showing a significant weakness in working memory but also in processing speed[92]. IQ score has been found to have a weak correlation with adaptive functioning in this population[93,94]. Furthermore, IQ score is significantly and inversely correlated with psychopathology. Therefore, children with moderate and severe intellectual disability experience greater psychiatric disturbance, and IQ scores below 50 indicate poor psychiatric outcomes[95].

Behavioral impairments

Behavioral problems of individuals with FASD are strictly connected with deficits in executive functioning resulting in difficulties in emotional regulation and adaptive functioning[66,73,96].

Self-regulation

Self-regulation refers to the ability to control behavior and manage thoughts and emotions in appropriate ways. Unfortunately, individuals with FASD can exhibit a variety of dysregulation problems including disruptions in attention, problematic behavior, poor academic performance and adaptive functioning, and low social competence[97-99]. FASD has been found to exhibit serious internalizing (e.g. depression) and externalizing (e.g., hyperactivity, antisocial behavior) behavioral problems that often persist in adolescence and adulthood[100,101], high rates of mood disorders[61] and oppositional defiant disorder, conduct disorder, and ADHD[102]. Importantly, ADHD is the most common psychiatric disorder diagnosed in children[103].

Behaviorally, children with FASDs have high also rates of social behavioral problems resulting from difficulties in social cognition and emotional processing[104]. They have problems dealing with overstimulation and the frequent occurrence of externalizing behaviors[105]. Furthermore, high rates of oppositional defiant disorder and conduct disorder often suggest severe difficulty following rules or controlling impulsive behaviors related to FASD[5,106]. Interestingly, a variety of research is providing evidence that early interventions targeting self-regulation and executive functions among children with FASD produce more effective and generalizable improvements than domain-specific interventions[107-109].

Adaptive functioning

PAE is often associated with a lower acquisition of life skills. Adaptive functioning, used to refer to skills related to daily living for personal and social sufficiency, is an area of special concern for children with FASD because these impairments are pervasive across domains and situations as children age[110]. There are three main areas of adaptive skills: social (e.g., communication, relationship development), practical (e.g., grooming, dressing, eating), conceptual (e.g., reading, writing), and motor skills for very young children[111]. Deficits in adaptive functioning skills have been reported across the spectrum of FASD and in all three domains[52,66,112].

Discussion

FASD is considered a "hidden disability" because most individuals affected by PAE are not identified until adolescence or adulthood, if at all[113-115]. Misdiagnoses have major repercussions for treatment, which can be ineffective because the brain of FASDs works differently from similar neurodevelopmental diseases[116]. The current diagnostic FASD guidelines have the important merit of providing criteria for making a diagnosis, but they are concerned with defining the severity of the neurodevelopmental impairments rather than also the specificity of the impairments across the spectrum[117].

This limit has impacted the diagnosis of ARND based primarily on the neurodevelopmental impairments rather than the characteristic facial traits and growth deficits associated only with FAS and pFAS. Unfortunately, 80-90% of cases of FASD are ARND representing a large FASD population that is often undiagnosed[118]. Since the cognitive and behavioral deficits seen in FASD are also common in other neurodevelopmental disorders, researchers have sought to identify a distinct neurobehavioral profile to facilitate the differential diagnosis of ARND. Nevertheless, all the studies on topic present significant methodological limitations, so that is not possible to define a neurocognitive and behavioral profile specific to FASD[119].

Conclusions

Preventing FASD begins with raising awareness among expectant mothers about the risks associated with alcohol consumption during pregnancy[25,120,121]. Education campaigns emphasizing the importance of abstinence from alcohol throughout pregnancy play a crucial role in preventing FAS. It could be quite useful also to analyze, during pregnancy the presence of ethanol metabolites in the mother biological samples (hair, urine) or in the meconium to really disclose alcohol abuse during gestation[24,122-127]. Healthcare providers also play a vital role by offering guidance and support to pregnant women, encouraging them to abstain from alcohol and providing resources for assistance if needed. Additionally, creating supportive environments that promote healthy lifestyle choices during pregnancy, coupled with policies that restrict access to alcohol among pregnant women, can contribute to the prevention of FAS and improve maternal and child health outcomes.

**Interdisciplinary Study Groups:* - Sapienza Università di Roma, AIDEFAD - Associazione Italiana Disordini da Esposizione Fetale ad Alcol e/o Droghe, SITAC - Società italiana per il trattamento dell'alcolismo e delle sue complicanze. SIFASD - Società Italiana Sindrome Feto-Alcolica, SIPPS - Società Italiana di Pediatria Preventiva e Sociale, FIMMG-Lazio - Federazione Italiana dei Medici di Medicina Generale Lazio, SIMPeSV - Società Italiana di Medicina di Prevenzione e degli Stili di Vita, CIPe - Confederazione Italiana Pediatri. Alberto Chiriatti, Alberto Spalice, Alessio D'Angelo, Andrea Agostini, Andrea Liberati, Antonella Cavalieri, Camilla Di Dio, Cinzia Di Matteo, Elena Pacella, Enrico Finale, Francesco Chiarelli, Francesco D'Antonio, Giampiero Ferraguti, Ginevra Micangeli, Lina Corbi, Lucia Ruggieri, Maria Grazia Piccioni, Maria Pia Graziani, Mario Vitali, Martina Peracchini, Michela Menghi, Monica Napolitano, Paola Ciolli, Patrizia Riscica, Pier Luigi Bartoletti, Raffaella Punzo, Roberto Paparella, Romolo Di Iorio, Simona Vescina, Stefania Pipitone.

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Corresponding author:
Marisa Patrizia Messina
E-mail: marisapatrizia.messina@uniroma1.it
Giovanna Coriale
E-mail: giovanna.coriale@aslroma1.it


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