Fetal Alcohol Spectrum Disorder (FASD): neurobehavioral profile, indications for diagnosis and treatment

Fetal Alcohol Spectrum Disorder (FASD): profilo neuro-comportamentale, diagnosi differenziale e indicazioni per il trattamento

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SUMMARY. It is now known that exposure to alcohol in utero produces a wide spectrum of morphological and behavioural outcomes in the offspring, commonly referred as fetal alcohol spectrum disorders (FASD). A large body of literature documents cognitive deficits and behavioural-emotional difficulties in children with FASD. Researchers have found that individuals with FASD often experience a range of adverse life outcomes, called secondary disabilities, which include disrupted school experience, troubles with the law, confinement, inappropriate sexual behaviours on repeated occasions, and alcohol/drug related problems. Additionally, despite considerable data published on cognitive and behavioural disabilities in children with FASD, relatively little information is available on behavioural or pharmacological interventions for alcohol affected children. This paper will provide a comprehensive review of the neuropsychological and behavioural effects of prenatal alcohol exposure, including a discussion of the emerging neurobehavioral profile. Finally, we will summarize published intervention studies of FASD focusing on their strengths and weaknesses.

KEY WORDS: Fetal Alcohol Syndrome Spectrum Disorders (FADS), neuropsychological problems, neuro-behavioral profile, differential diagnosis, behavioral approaches, psychopharmacology.

RIASSUNTO. È oramai scientificamente riconosciuto come l'esposizione in utero all'alcool possa provocare nel nascituro un'ampia gamma di effetti negativi morfologici e comportamentali nota come Fetal Alcohol Spectrum Disorders (FASD). Esistono numerose evidenze che attestano la presenza nei bambini FASD di disturbi nel dominio cognitivo, comportamentale ed emotivo determinati dall'esposizione prenatale all'alcool. Molti ricercatori hanno inoltre riscontrato nell'adolescenza e in età adulta la presenza di disabilità secondarie vale a dire esperienze scolastiche negative, problemi con la legge, comportamenti sessuali non appropriati e alcolismo che pregiudicano molto la loro qualità di vita. Nonostante siano stati pubblicati molti articoli sui problemi cognitivi e comportamentali, poco si è fatto per capire quale sia il trattamento comportamentale e farmacologico che funzioni di più su questa popolazione clinica. Questa rassegna fornirà informazioni sugli effetti neuropsicologici e comportamentali dovuti all'esposizione prenatale all'alcool e sui profili neuro-comportamentali che si stanno sviluppando per sostenere la diagnosi e l'intervento. Inoltre, verranno date informazioni sui trattamenti comportamentali proposti in letteratura, analizzandoli nei loro punti di forza e di debolezza.

PAROLE CHIAVE: disordine dello spettro feto-alcolico (FASD), problemi neuropsicologici, profilo neuro-comportamentale, diagnosi differenziale, interventi comportamentali, psico-farmacologia.

INTRODUCTION

Fetal Alcohol Syndrome (FAS) is the most extreme fetal alcohol induced pathology, following consumption of alcoholic beverages during pregnancy (1,2). Although alterations in physiologic parameters (height, weight, and cranial circumference), and abnormalities in facial structure are prominent signs of the full blown syn-

drome, the central nervous system damages are more dramatic and invalidating since they compromise a regular neuro-behavioral development. Evidence from animal studies (3) and on human subjects (4) shows a great variability in the way the use of alcohol during pregnancy affects the fetus. The degree of variability depends on several factors: quantity of consumption, modalities of consumption (continued use vs. binge drinking), time frame of alcohol consumption (i.e. first, second, third trimester), mother's age, body mass index, genetic make-up, post natal variables (e.g. adequate neonatal nutritional intake, socio-cultural status, and variety and quality of environmental stimuli (5-7). FASD (Fetal Alcohol Spectrum Disorders) definition, even though not exactly diagnostic, is applied to the entire gamut of the negative consequences in the offspring of mothers drinking during pregnancy: physiologic, behavioral, and neuro-cognitive abnormalities. As compared to FASD, FAS represents the extreme manifestations of the spectrum, which could lead to fetal death (8-11) (**Figure 1**). In reality, all FASD children may show similar behavioral and cognitive deficits (12,11). The spectrum of deficits is quite large, including cognitive problems, executive functions disregulation, memory impairment, learning problems, language disorders, visual-spatial deficits, motor impairments, attention deficits problems, and also psychopathology, and secondary disabilities (11,13,14).

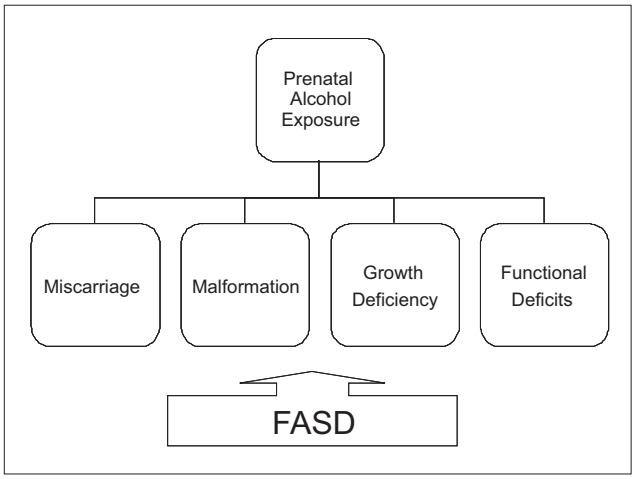

Figure 1. Spectrum of consequences of fetal alcohol exposure.

COGNITIVE AND BEHAVIORAL PROBLEMS WITH FASD: REVIEW OF LITERATURE

Overall intelligence

Although alcohol abuse during pregnancy is the main non-genetic cause of mental retardation, the majority of FASD subjects does not show cognitive delays but an IQ score at the lowest normal range (average score: 70) (15-18). Overall intelligence seems to be inversely related to the presence of facial dysmorphia and growth retardation: many individuals prenatally exposed to alcohol show intellectual deficits even in the absence of typical FAS facial characteristics in its extreme form (i.e. smooth philtrum, short palpebral fissures) and growth delays. However FAS children seem to have more pronounced intellectual deficits (11,19).

Executive functioning

Executive functioning refers to the ability to develop and retain appropriate problem solving strategies to attain objectives and goals (20). A good executive functioning depends on intact cognitive functions related to the ability for planning, response inhibition, working memory and the involvement of more basic cognitive processes like attention span, memory functions, perceptual and motor activities (21). Executive functions depend on subcortical-frontal circuits, as the frontal lobes are connected to the basal ganglia and to the thalamus, areas which are extremely sensitive to the exposure of alcohol during the prenatal period (22,23). Generally, individuals with FASD show planning and problem solving deficits (24), difficulties with abstract thinking and with shifting to subsequent conceptual categories (19,25), problems with the ability to inhibit their responses to stimuli (26,27), and difficulties to maintain and manipulate information in the working memory (24,28,29).

Memory and verbal learning

FASD children show a great deal of difficulties in the area of verbal learning (30). In one study by Mattson, the researchers tested the subjects with a list of words (CVLT-C) to evaluate their learning and memory abilities with unstructured tasks. The FASD children were able to recall fewer words than the control group in the learning and memory phases (free recall after 5 and 20 minutes). However, the reduced quantity of integrated information was retained. These results show that the deficits in verbal memory, seen in FASD children, stem from a problem of encoding information rather than from a memory problem (difficulty in retrieving information): once the information is elaborated it will be retrievable in the future. FAS children show the same learning problems in non verbal abilities. Hamilton et al. (32) evaluated the area of spatial learning navigation

abilities utilizing The Morris Water Task. As compared to the control group, the FASD group showed lower level of performance, similar to those observed in the same test in mice who were prenatally exposed to alcohol or whose Hypothalamus was damaged.

Language and visual-spatial abilities

FASD children show peculiarities in the areas of receptive and expressive communication (35): neuropsychological evaluations show both deficits in the areas of language production and comprehension, but the latter seems to be most affected. In a control study in Italy (16-18) in children enrolled in first grade, comprehension ability was evaluated with the Rustioni Test (36). FASD Children (n=45) showed significantly lower comprehension scores than those of the non-exposed group (n=117). Retrospective studies have shown so far, both expressive and receptive language problems (17,37) but the results of prospective studies are less clear (38). The level of prenatal exposure to alcohol could explain the discrepancy in outcomes: the majority of studies has focused on children exposed to low levels of alcohol. It is possible that the language problems become visible only after more a consistent exposure to alcohol, or alternatively, that they are a consequence of more general cognitive dysfunctions (37).

FASD children show visual-motor deficiencies (39), suggesting praxic-constructive deficits. Moreover, they show difficulties in elaborating local versus global characteristics in a context of visual stimuli (31).

Motor functions

Many studies have shown a clear association between prenatal alcohol exposure and motor deficits. In particular, deficits are apparent in the areas of gross motor skills (involving the whole body) and fine movements (involving the hands). However, it is not clear if the motor deficits are permanent. Hypothetically FASD children could naturally outgrow motor system deficits (11). However; additional studies are needed to gain more insight into these aspects.

Attention

FASD children frequently reveal attention deficits on vigilance, reaction time, and information elaboration tests. It seems that attention deficits, affecting more than 60% of FADS subjects, may have a high probability of morphing into Attention Deficit and hyperactive disorder (ADHD). In an Italian study (16-18), including first grade children, attention and hyperactive deficits were evaluated exclusively by utilizing the attention deficit and hyperactivity scales in the Pelham Disruptive Behavior Disorder Rating Scale (41). Both teachers and parents evaluations revealed in the FADS sample (n=45), more attention problems than in the non-exposed group (n=117), while they did not identify any significant difference in regards to impulsive behaviors. When we evaluated the statistical impact of attention problems on language comprehension, non-verbal reasoning and school performance we didn't found significant differences between the groups regarding the cognitive ability under investigation. Therefore, the FASD group presented essentially attention deficits affecting negatively the other cognitive areas investigated in the study.

Behavioral problems

Cognitive deficits identified by neuropsychological testing, if not timely treated, may contribute to a variety of behavioral problems, known as secondary disabilities (**Figure 2**). These are not present at birth, but are consequences of primary disabilities. Longitudinal studies have shown that FASD adolescents have a higher chance of developing secondary disabilities including mental health issues (90%), inappropriate sexual behaviors (49%), legal problems (60%), below average school performance and dropping out of school

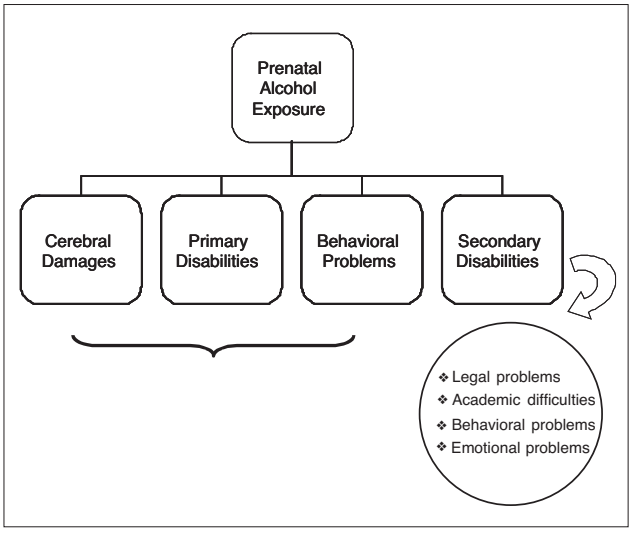

Figure 2. Primary and Secondary Disabilities.

(60%), substance abuse and alcohol related problems (33%) (42,43).

As time goes by, FASD subjects eventually develop self and socially damaging behaviors. Family dynamics, socioeconomics, and culture could represent either protective factors or contribute to exacerbating the expression of secondary disabilities (44).

School performance

A large body of studies has revealed learning problems in both verbal abilities and mathematics (45). The ability to perform on mathematical skills seems to be the most vulnerable area to the prenatal exposure to alcohol. The major difficulties seem to be related to the ability for numerical elaboration (46).

Adaptive behavior

Adaptive functioning defines the ability to function responsibly and independently (47). Individuals familiar with the subject under evaluation, complete the questionnaires related to the evaluation of his/her daily level of functioning: ability to take care of personal hygiene and to get dressed without help, to display appropriate social behaviors, to use appropriate language, to manage efficiently their free time. FASD subject tend to show marked deficiencies in the area of adaptive behavior. Areas like social skills and interpersonal relationships seem to be particularly compromised (48). Greenbaum et al. (49), in a study dating back to 2009, has pointed out a major difficulty in FASD subjects as compared to their peers, in regards of their ability to identify emotions using nonverbal cues, as facial expressions and tone of voice. Also, it seems like the difficulties in emotional identification tend to increase according to the complexity of the stimuli: rapidly evolving emotional states or situations characterized by blurred or ill-defined emotional characteristics are not well managed by FASD subjects. Often adaptive and social difficulties are related to preexisting cognitive deficits. FASD subjects may not be able to comprehend the social meaning of a conversation mainly because of linguistic problems. They may manifest difficulties in distinguishing reality from fiction or in understanding the use of humor or irony expressed by the person they are conversing with. Other problems could arise from difficulties in abstract thinking, and memory problem, which could, in turn, translate into misunderstandings and problems in social interactions.

Emotional functioning

A great deal of studies has shown the presence of emotional problems both in FASD children and adults (50). They show both problems with behavioral regulation and mood stability. They can shift rapidly from being excited to being sad and angry. Anger and impulsivity often result in temper tantrums and aggressiveness. Other emotional difficulties can include perseverations of ideas and actions.

NEUROBEHAVIORAL PROFILE AND DIFFERENTIAL DIAGNOSIS

Alcohol related fetal abnormalities are usually classified in 5 distinct diagnostic categories:

1. FAS (Fetal Alcohol Syndrome), with documented maternal exposure to alcohol, characterized by a triad of symptoms: facial dysmorphism, growth delays, anomalies in central nervous system development;
2. FAS, without clear documentation of maternal exposure to alcohol, but still showing the typical triad;
3. Partial FAS, characterized by the presence of some of the facial abnormalities along with either a growth delay and central nervous system anomalies, or cognitive and behavioral problems;
4. ARBD (Alcohol-Related Birth Defects) characterized by presence of congenital malformations and dysplasia due to the noxious effects of alcohol;
5. ARND (Alcohol-related Neurodevelopmental Disorders): complex entities which include both behavioral and cognitive abnormalities (1,2).

The diagnosis of full syndrome or partial FAS does not necessarily require clear documentation of use or abuse of alcohol during pregnancy. In ARND children the distinctive facial characteristics and the growth delays are absent. To reach a diagnosis of ARND is necessary the presence of neurobehavioral problems along with mother's report of alcohol use during pregnancy. Usually mothers are reluctant to report alcohol use during pregnancy because of problems related to social acceptance and stigma, and the emotional issues stemming from being responsible for FAS in the offspring. Since ARND subjects represent about 80% to 90% of the FASD group (18,51), it follows the need to build a neurobehavioral profile that defines the FASD group. Moreover, ARND subjects could easily be confused with other pathologies (i.e. learning disabilities, or ADHD (Attention Deficit Hyperactive Disorder). Therefore it is essential to make a differential diagnosis.

Neuro-behavioral profile

The vast literature on FASD cognitive and behavioral impairments does not provide a clear picture of a specific neuro-behavioral profile defining the unique clinical manifestations of FASD. Mattson et al. (52), compared the response to neuropsychological testing of FAS alcohol exposed children, non-FAS exposed children (ARND group), and non-exposed children (control group). The results showed that a common set of neuropsychological abnormalities distinguished both FAS and non-FAS exposed subjects from the control group. The two clinical group (FAS-ARND) had difficulties in working memory, verbal fluency, planning abilities, flexibility, attention span, spatial reasoning and emotional regulation. Kodituwakku (53,54), on the other hand, have proposed a model based on the concept of a generalized deficit in elaborating information as the basis for the specific deficits in FASD. The deficits in cognitive functioning, the slow processing of information, and the difficulty with complex tasks, characteristic of FASD would be related, according to the author, to a generalized deficit. However, Nash et al. (51) defines in detail the FASD behavioral profile, as characterized by attention deficits and hyperactivity, similar to those seen in ADHD. in contrast to ADHD subjects, FASD children also show difficulties in their capacity to experience guilt and are prone to cruel and infantile behaviors.

Differential diagnosis

The most recent scientific work on the subject has focused on comparing FASD children with other pathological syndromes sharing similar behavioral characteristics, with the goal of defining more precisely a distinct FASD neuro-behavioral profile. Specifically, the studies comparing children with FASD to non-exposed children with ADHD and non-exposed children with low IQ scores lend support for a specific neurobehavioral profile associated with prenatal exposure to alcohol.

FASD e ADHD

The percentage of FASD children diagnosed with ADHD is related to the degree of alcohol consumption during pregnancy. The prevalence of ADHD in FAS children is between 49,4% and 94% (43). In general FASD subjects have a 70% probability of developing problems with attention and hyperactivity (51). Even though FASD subjects with ADHD, and ADHD subjects seem to belong to the same group, studies have shown that their neuro-behavioral profile is substantially different. Attention Deficits tend to persist during adolescence and adulthood, and compared to hyperactive behaviors they are more common in FASD–ADHD subjects than in the non-FAS-ADHD (16,17,23,55). The ability to engage in adaptive behavior shows deficits in both populations, with some differences. In a study by Crocker et al. (56) three groups (non-FASD ADHD, ADHD-FASD and children with normal development) were compared using the Vineland Adaptive Behavior Scales (57). In comparison to the ADHD group, FASD subjects showed lower performance level in their social and communication skills. In the daily life skills domain, the ADHD group showed more difficulties as compared to the FASD group. Moreover, FASD subjects, as compared to the ADHD group, showed a negative correlation between age and their score: the deficits in the area of adaptive functions show deterioration as they grow older. In another study by Nash et al. (51), FASD subjects (FAS= n=11; ARND n= 43) were compared with an ADHD group (n=30), on the Child Behavior Check list (CBCL) (58,59) with the goal of assessing behavioral problems. Both groups showed attention and hyperactive deficits. However, the FASD subjects, as compared to the ADHD group, showed a more pronounced tendency to be devoid of guilty feelings, to engage in cruel and more immature behaviors, and stealing. In regards to their adaptive abilities, both groups showed problems in socializing and communicating. While the ADHD essentially showed developmental delays, the FASD subjects, in general, do not seem to improve as they get older. Moreover, FASD subjects showed difficulties with their daily-living skills, social cognition, and their ability in identifying emotions using non-verbal cues (e.g. facial expressions). In regards to cognitive functions, many studies have shown differences in the features of attention deficits. Coles et al. (60) have reviewed the level of attention in FASD and ADHD groups implementing Mirsky's four factors model. While FASD children showed deficits in the process of encoding and attention shifting, the ADHD group showed more problems in the areas of sustained and selective attention. Moreover, as compared to the FASD group, the ADHD group showed a very limited ability to inhibit their response on the GO/NO-GO tests. Also, the two groups, in general, show similar executive functioning on the WCST (Wisconsin Card Sorting Test), but only FASD children show deficiencies on the letters fluency test and on the TMT (Trail Making Test). Verbal learning shows deficits in both groups. The nature of the deficits differs: In the FASD group the learning deficit is related to difficulties with the encod-

ing process, in ADHD children the problem stems from a deficit in recalling stored knowledge (62).The monitoring of motor functions and sense of equilibrium are differently damaged. Both groups show difficulties on test measuring complex motor and equilibrium functions; however FASD subjects, as compared to ADHD subjects, show intact basic motor abilities (63).

Comparison between IQ-Matched groups

The comparison between FAS children and non-alcohol exposed children both showing a low IQ, has revealed both similarities and differences in their neurobehavioral profile. Both groups have difficulties with receptive and expressive language functions, with attention span and in retaining verbal information. FAS subjects, as compared to the non-exposed group, show more deficits in the assessment of their externalized behaviors (attention deficits), their adaptive abilities, and their verbal learning (11).

FASD TREATMENT

Both researchers and clinicians agree that the frequent deficits related to FASD can result from the effects of multiple factors (64). Besides alcohol exposure, these babies can be exposed to other prenatal risk factors, as teratogenic substances (i.e. neuroleptics, street drugs), to inadequate prenatal care, to poor maternal nutritional status, or to maternal stress during pregnancy. Also, the postnatal period of development could be at risk if the baby is exposed to parental behaviors characterized by substance abuse, mental problems, conflictual relationships, and domestic violence. Statistically, FASD children are at 10 to 15 % higher risk to spend time in temporary custody. Actually many adopted children have FASD (65).The variability of risk factors for FASD subjects makes them a heterogeneous group in terms of the etiopathology and therefore difficult to treat with a homogeneous clinical approach. Since the effectiveness of treatment depends on an adequate neuropsychological evaluation, capable of identifying the strengths and weaknesses of children with deficits, FASD children are in need of a thorough and specific diagnostic assessment. On the other hand, the early individuation of FASD children is another challenge to face in order to develop effective intervention programs. The providers working in different medical settings (i.e. obstetricians, primary care physicians, pediatricians), do not ask usually pregnant mothers if they are consuming alcohol, and there are few physicians able to identify the dysmorphological features defining the syndrome; very few medical centers have the expertise to identify and diagnose FASD. These factors combined with others contribute to a delay of FASD diagnosis reducing therefore the benefits of early intervention. According to Streissguth et al. (50) early diagnosis is the most important predictor of good treatment outcomes, also because greatly reduces the development of secondary disabilities. Even though, in the past few years, many studies have been published on the cognitive and behavioral disabilities characterizing FASD, just few data are available on their treatment (54). Moreover, the published works show some methodological limitations: small samples, which affect the generalization of the findings; few studies have included follow ups to evaluate the stability of outcomes; the majority of them has focused on school age children. And very few have focused on early infancy, adolescence, and adulthood (66). Despite these limitations recent studies focusing both on animals and human beings have shown interesting insights regarding treatment

Animal studies

The majority of studies including prenatally exposed animal have shown that an environment richer in prenatal care (67), or richer in stimuli (68), or giving the possibility of practice a specific skill (e.g. motor abilities) (69), or providing a diet richer in antioxidants (5-7), tends to minimize the noxious effects of alcohol exposure suggesting the plasticity of the central nervous system when there are favorable contextual factors and timely therapeutic interventions.

Human beings studies

A review of literature shows specific focus on four fundamental areas of research: interventions on parents, cognitive and educational approaches, training in coping skills, and pharmacologic interventions.

Interventions with parents

Recent studies have identified a high level of distress in FASD offspring's parents (70,71). Because of their behaviors, emotional, and cognitive problems, FASD children can create serious issues for parents. Moreover, mothers, who may themselves have alcohol abuse issues, may also be a source of anxiety for them, contributing to establishing dysfunctional relationships. Of

course, dysfunctional relationships between parents and offspring could create problematic issues and situations difficult to manage. Olson (72) has developed and applied the Families Moving Forward model (FMF Model), with the goal of improving the sense of self-efficacy for parents taking care of their children, and ameliorating their behavioral problems. This model of consultation has two main objectives: 1) Teaching parents strategies focused on environmental modifications with the goal of improving their ability to engage in positive behaviors; 2) Educating parents on the problems experienced by FASD children. Unfortunately, these behaviors are often interpreted by parents as whims or purely oppositional and cause additional relationships problems. For example, explaining that FASD children "bad behavior" is a consequence of neuro-behavioral deficits on which they have minimal control, helps remarkably in lowering parental distress (Psycho-Educational Intervention). Olson (72), to evaluate the efficacy of his model, conducted a study which included 52 FASD children (age 5-11), and their parents. All the children displayed substantial deficits in their executive functions and behavioral problems. At the end of treatment, which lasted between 9 and 11 months, FASD children showed a substantial reduction of behavioral problems and their parents increased ability in using caring skills and being more receptive to their needs. In another work by Grant et al. (73), mothers with alcohol and substance abuse problems, were the only recipient of therapeutic intervention, with no focus on the offspring. While positive effects have been found for mothers, at a three-year follow-up, no significant differences were found between the treatment and control group children on a measure of developmental functioning. Generally if the treatments focus on the family, other than on the children, they seem to have greater efficacy (54,66). Bertrand has identified two factors responsible for the effectiveness of treatment: the parenting training and the treatment of cognitive and behavioural deficits of children (72). Kodituwakku (54) proposes a more contextual model whose positive outcomes depend from its inclusion of social (i.e. family, school, community), biological and neuro-behavioral factors. Kodituwakku stresses that early training in cognitive and self-regulation skills produces better outcomes than interventions on specific cognitive deficits, since helps children in displaying more appropriate behaviors with their peers and contributes to behavior fostering learning abilities. Since FASD children have a generalized deficit in the processing and integration of multiple elements or relations, a step wise approach utilizing more complex tasks and the presentation of information at a slower rate, use of concrete examples, and repetition of information could be included in the training program. Also, since stressful social problems and poverty are very frequent with FASD children, socio-economic interventions, including job orientation and training, could be considered as part of a dynaminc treatment plan (54). Those life stressors, stemming from a very fragile sense of attachment, abusive behaviors and violence, may trigger an over-activation of the hypothalamic hypophyseal axis (HPA), which may contribute to the inability for self-regulation in children (71). Since prenatal alcohol exposure has negative effects on the HPA axis (74), FASD children have a higher probability to develop emotionally disturbed behaviors due to their inability to control emotions. These new insights have important implications as they indicate the need to provide families with emotional support. Kodituwakku (54) has suggested that an intervention based on a combination of both parental support and focus on the children constitutes the foundations for good treatment. Adding pharmacologic approaches aimed at controlling behavioral and emotional problems constitutes a helpful strategy in many cases.

Cognitive and educational interventions

As already described, FASD children show deficits in the areas of verbal and spatial learning, planning, cognitive flexibility, work memory, response inhibition, problem solving, reading and mathematical skills (52). Academically, FASD children frequently show learning deficits and behavioral problems (75), and are frequently suspended from school (76). Therefore, it is pivotal that teaching strategies and environmental modifications are carried out to address them (77). At the same time, there is a need for planning interventions helping children to face learning, cognitive, and behavioral problems. Adnams (78) has conducted a study to evaluate the effects of Cognitive Control Therapy (CCT) in reducing behavioral and learning problems in FASD children. CCT involves children in progressively more challenging tasks, including awareness of body movements in relationship to the environment and the ability to organize information (79). Therefore CCT techniques are complementary to self-regulation training since they facilitate the development of cognitive and sensory-motor functions with the goal of reaching a higher level of control. In Adnams study (78), the intervention group received one hour a week of CCT for the duration of 10 months. The control group was involved in the mainstream approach based on standard group lectures. Both groups received a pre-post intervention evaluation, with a battery of cognitive tests focusing on their cognitive, aca-

demic and behavioral abilities. The intervention group showed improvements, as compared to the control group, in behavioural, academic abilities, level of motivation, and self-efficacy, according to the feedback provided by therapists and teachers. However, few of these changes were confirmed by post treatment evaluation. Loomes et al. (80) tried to understand if the work verbal memory in FASD children could benefit from a process of repetition of information. The 33 children (age 4-11) involved in the study were assigned to the intervention and control groups. The intervention group showed an improvement on the performance of tests evaluating numerical attention span (MBT span is related to the ability to show immediate recall of a number of stimuli in the order in which they were presented: the higher the number of correct responses the higher the subject's MBT ability). Chasnoff (72), utilized an already established neurocognitive training program, known as the "Alert Program" (81) to treat problems with self-regulation and executive functioning in 78 FAD children (ages 6-11), who had been adopted or given away for adoption. Treatment completion showed a significant improvement in the treated deficits. Kable et al. (82) developed a sociocognitive program for FASD children showing problems with mathematics. Before assigning the children (n=56, ages 3-10) to the intervention and control groups, their parents were involved in a two-day workshop where they received information on how to help their children to monitor their behaviors. Later on, only the parent- intervention group received training to be actively involved in the mathematics teaching program. The intervention group showed a significant improvement, as compared to the control group not only in their mathematical skills, but also in their behaviors.

Training in adaptive abilities

FASD children show adaptation deficits, including those related to communication, socialization, personal and social skills, which sometimes may be much debilitating than cognitive problems (83). O'Connor et al. (84) adapted a training program focusing on social skills, the Children's Friendship Training (CFT) (85), for a group of FASD children (age 6-12). CFT is a group-based intervention that teaches social skills to help children be accepted by others rather than rejected and includes parents in the role of social facilitators. O'Connor's intervention focused on the following areas: conflict management and negotiation, playing activities at home and with peers. The behavioral techniques used were: modeling, rehearsal and coached practice with performance feedback during treatment sessions, rehearsal of skills at home, homework assignments and coaching by parents during interactions with peers. Results showed that at the end of the program, the CFT group had improved social knowledge of appropriate social behavior and showed fewer problem behaviors than the control group.

Pharmacologic intervention

FASD children often show a high incidence of diagnosed psychiatric problems. Indeed more than 80% of them meets the criteria for a psychiatric diagnosis (86).

Attention deficit and hyperactive disorder are the most common entities associated with FASD (71). The development of both dopaminergic and noradrenergic systems can be seriously damaged by the prenatal exposure to alcohol. This seems to be one of the reasons for the association of attention deficits, hyperactivity, and impulsivity with FASD (87). However, there is a paucity of studies focusing on the efficacy of medications for ADHD in FASD children. Stimulants like metylphenitade, and dextroamphetamine, and non-stimulants like atomoxetine, tryciclics antidepressants, and alfa -2-adrenergic agonists have been used to control behavioral problems in FASD children (88-91). Oesterheld et al. (92) reported the positive effects of metylphenidate on hyperactivity and impulsivity but no tangible effects on inattention. Moreover, several side effects were recorded, and one in four children had to leave the study because of excessive weight loss. Snyder et al. (93) compared the effects of three psychostimulants (methylphenidate, dextroamphetamine, and pemoline) with placebo. The results showed positive effects on behaviors (as viewed by parents), but not on sustained attention. Frankel et al. (94) conducted a study to evaluate the interaction between psychosocial treatment and medications. He enrolled 77 FASD children (40 males; 37 females. Ages: 71-139 weeks). All of them received social skills training and psychopharmacologic treatment. Twenty eight children received stimulant therapy (amphetamine), thirteen received neuroleptics (risperidone, olanzapine), ten received antidepressants (paroxetine, fluoxetine, mirtazapine), eight received non-stimulant medications commonly used in treating ADHD (clonidine and atomoxetine), four mood stabilizers, and fourteen did not receive any pharmacologic treatment. Those children on neuroleptics did better than those on stimulants. In conclusion, from the few studies available, it seems that symptoms related to hyperactivity and impulsivity respond better to pharmacologic treatment, than those

related to attention problems, and that the combination of psychosocial interventions and neuroleptics yields better results than separate treatments.

CONCLUSIONS

Alcohol is a culturally and socially accepted teratogenic substance whose social consumption and abuse are widely spread. Although scientific data show that the abuse of alcohol during pregnancy is one of the most well-known non-genetic causes of mental retardation and one of the most pivotal public health issues, the majority of FASD subjects does not show intellectual delays. FASD children show executive functioning deficits (i.e. problem solving, planning abilities), verbal memory deficits (due to encoding problems), production, and in particular, comprehension language problems, deficits on visual-motor testing, both gross and fine motor difficulties, attention deficits (12,11). These cognitive deficits, when not timely treated, could cause "secondary disabilities", appearing later in life, and including legal problems, academic difficulties, dysfunctional behaviors, and emotional problems (42,43). Therefore, early diagnosis is of vital importance: a clear and definitive FASD diagnosis, before the age of six is usually associated with a substantial decrease in the incidence of secondary disabilities. In addition, both early diagnosis and specific interventions can lessen the intensity of its pathology and the progression of the associated secondary disabilities. The literature reviewed in this article shows a detailed picture of the current treatment modalities for FASD (54,66,72). Most probably, the lack of exchange and integration among different philosophies of research has been a limit to the possible benefits which could derive from a collaborative approach. Also, independently from the presence of functional deficits, careful consideration of the child developmental stages is paramount. Therefore, parental involvement is essential because they are primary agents in the developmental growth of their offspring. Integrated models of intervention, including educators' psycho-educational training may yield more positive and generalizable outcomes. In conclusion, the peculiar features and characteristics of FASD require a multi-level and multi-disciplinary approach both in the evaluation and therapeutic phases.

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