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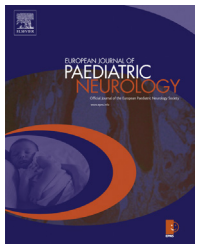

Review article

Diagnosis of fetal alcohol syndrome (FAS): German guideline version 2013

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ABSTRACT

Background: Fetal alcohol syndrome (FAS) belongs to the umbrella of fetal alcohol spectrum disorders (FASD) and affects 0.02–0.8% of all annual births with a high number of undetected cases. FAS has severe and life determining consequences for the affected individual and his family.

Aim: The aim of the German guideline version 2013 is to provide objectively evaluated, evidence-based, clinically relevant and easily applicable diagnostic criteria for the full picture FAS.

Methods: A systematic literature review (2001–2011), analysis of international guidelines and focused hand search were performed. Based on the evidence-assessed literature the multidisciplinary guideline group (14 German Professional Societies, the patient support group "FASD Germany" and 15 additional experts) consented recommendations for the diagnosis of FAS.

Results: The following diagnostic criteria for FAS resulted: at least one deficit of growth, three defined facial characteristics and one functional or structural anomaly of the central nervous system. Confirmation of intrauterine alcohol exposure is not considered as a prerequisite for FAS diagnosis.

Conclusion: The German guideline presented here constitutes an unbiased evidence-based approach to the diagnosis of patients with fetal alcohol syndrome. It includes a practical pocket guide FAS for a quick overview of the diagnostic workup in everyday clinical work.

Contents

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1. Introduction

Injuries to health induced by intrauterine alcohol exposure are summarized under the term fetal alcohol spectrum disorder (FASD). FASD includes fetal alcohol syndrome (FAS), partial fetal alcohol syndrome (pFAS), alcohol related neurodevelopmental disorders (ARND) and alcohol related birth defects (ARBD).

The work we present here is a first step in developing criteria for diagnosis of the full range of FASD. Here we focus on the development of criteria for the full picture of FAS only and not for the other three categorical diagnoses of FASD.

Fetal alcohol syndrome (FAS) is a common and often not recognized disorder. It is completely avoidable. According to the international literature of the last 10 years the prevalence of FAS ranges from 0.2 to 8.2 per thousand births. The annual birth rate in Germany is approximately 678,000. That means that 130 to 5400 babies with FAS are born in Germany every year. Consequently 2340 to 97,200 children and adolescents (0–18 years of age) actually live in Germany and most of them are undiagnosed.

FAS has severe consequences not only for the affected individual and his or her family but also for the immediate developmental and educational environment and for the health and social systems in general.

FAS can be seen as a “toxic static encephalopathy”. While the cerebral damage due to intrauterine alcohol exposure is irreversible, the impairment of functioning in every-day life changes during development and can be positively influenced by early conceptualization and individually appropriate stimulation and training (e.g. Ref.[1]). Thus FAS also meets the classical criteria for a “developmental disorder”.

The German guideline presented here provides evidence-based, clinically relevant and in practice easily applicable diagnostic criteria and recommendations for the identification of FAS in children and adolescents.

Implementation of this Guideline will be a first step to increase awareness in the (German) society for the severe complications of intrauterine alcohol exposure with the aim to reduce the prevalence of alcohol consumption during pregnancy and thereby diminish the incidence of FAS. Furthermore this guideline should assist in providing early and individual support and treatment of affected patients and their caregivers. The development of diagnostic criteria for the other fetal alcohol spectrum disorders (partial FAS, ARND and ARBD) is planned.

2. Methods

The German Federal Ministry of Health (GFMOH) initiated and partly financed this guideline project which was coordinated by the first and last author. The funding by the GFMOH did not influence the content of the guideline in any way.

In 2011, a guideline consensus group was established including representatives of the German Federal Ministry of Health, the German Scientific Societies and Professional Associations, the national Patient Support Group FASD Germany as well as additional FAS experts (Table 1).

Systematic retrieval of the literature and determination of levels of evidence (according to the Oxford Classification System 2009) were conducted by the guideline steering group in Munich and the AQuMed (German Agency for Quality in Medicine). The AWMF (Association of the Scientific Medical Societies) was responsible for the methodological guidance.

The key question for the systematic literature review was: Which development-related criteria enable the diagnosis of FAS in childhood and adolescence (0–18 years of age)?

The search included English and German literature published between January 1, 2001 and October 31, 2011 (search strategy and previously defined criteria for inclusion and exclusion of abstracts and publications see ePub: Tables 1 and 2). Full text publications included for evaluation were assessed for the levels of evidence provided using the Oxford Evidence Classification System 2009 (ePub: Table 3).

According to the level of evidence provided in the literature (from LoE 1 to LoE 5), a grade of recommendation (from the strongest recommendation A “we recommend” to the strong recommendation B “we suggest” to the recommendation grade C “may be considered”) was proposed by the guideline coordinators according to the schema of the German Association of the Scientific Medical Societies (Fig. 1). Depending on the clinical relevance, ethical considerations and practicability of the diagnostic criteria the multidisciplinary guideline group discussed and if required adapted the proposed grades

Table 1 – Members of the guideline-consensus-group.

German scientific societies and professional associations	Representatives
German Society of Pediatrics and Adolescent Medicine	Prof. Florian Heinen, MD
Society of Neuropediatrics	Prof. Florian Heinen, MD
German Society of Social Pediatrics and Adolescent Medicine	Juliane Spiegler, MD
German Society of Gynecology and Obstetrics	Prof. Franz Kainer, MD
German Society of Neonatology and Pediatric Intensive Care	Prof. Rolf F. Maier, MD
German Society of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy	Prof. Frank Häßler, MD
German Society of Addiction Research and Addiction Treatment	Regina Rasenack, MD
German Society of Addiction Psychology	Prof. Tanja Hoff
German Society of Addiction Medicine	Gerhard Reymann, MD
German Society of Midwifery Science	Prof. Rainhild Schäfers, MD
German Association of Midwives	Regine Gresens
German Association of Psychologists	Laszlo A. Pota
German Association of Pediatricians	Nikolaus Weissenrieder, MD
German Association of Physicians of the Public Health Services	Gabriele Trost-Brinkhues, MD

Function	Experts
Director of the children's home Sonnenhof	Gela Becker
Bavarian Academy of Addiction and Health Questions	Beate Erbas, MD
FASD Center, University of Münster	Reinhold Feldmann
Neonatology und Neuropediatrics, Ludwig Maximilians University Munich	Anne Hilgendorff, MD
Medical Director of the KMG Rehabilitation Center Sülzhayn	Heike Hoff-Emden, MD
Board Member of the German Society of Social Pediatrics and Adolescent Medicine	Ulrike Horacek, MD
Director of the German Association of the Scientific Medical Societies (AWMF-IMWi)	Prof. Ina Kopp, MD (nonvoting)
FASD Center, Neuropediatrics, Ludwig Maximilians University Munich	Mirjam Landgraf, MD
President of the Patient Support Group FASD Germany	Gisela Michalowski
Board Member of the Patient Support Group FASD Germany	Veerle Moubax
German Agency for Quality in Medicine (AQuMed)	Monika Nothacker, MD (nonvoting)
Youth Welfare Office Munich	Carla Pertl
Institute of Medical Information Processing, Biometrics and Epidemiology, Ludwig Maximilians University Munich	Eva Rehfueß (nonvoting)
Department for Health and Environment of the capital Munich, Health prevention for children and adolescents	Monika Reincke, MD
Neonatology, Ludwig Maximilians University Munich	Andreas Rösslein
Advocate for Child and Adolescent Rights	Gila Schindler
Medical Director of Neonatology, Ludwig Maximilians University Munich	Prof. Andreas Schulze, MD
Child and Adolescent Psychiatry, FASD Center, Heckscher Clinics, Munich	Martin Sobanski, MD
FASD Center, Charité University Berlin	Prof. Hans-Ludwig Spohr, MD
Child and Adolescent Psychiatry, FASD Center, Heckscher Clinics, Munich	Penelope Thomas
FASD Center, Charité University Berlin	Jessica Wagner
Board Member of the Patient Support Group FASD Germany	Wendelina Wendenburg, MD

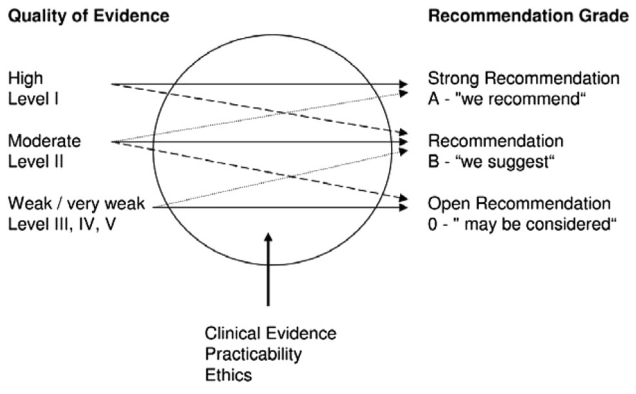

Fig. 1 – Consensus process based on the evidence-assessed literature.

of recommendation to reach official consensus. Guided by an independent methodologically experienced moderator (Prof. Ina Kopp, MD), formal consensus was obtained in the course of a nominal group process at three multidisciplinary consensus meetings (2011 and 2012).

3. Results

The systematic search in Pubmed resulted in 1363 and in the Cochrane Library in 20 hits. After application of the inclusion and exclusion criteria 178 full text publications were included for the assessment of evidence (ePub: Fig. 1).

The formal consensus process based on the evidence-assessed literature led to seven key recommendations for the diagnosis of FAS in children and adolescents (Table 2). Background information and additional recommendations for the performance of the key recommendations are given.

Table 2 – Key recommendations for the diagnosis of FAS.

Diagnostic recommendations	Level of evidence	Grade of recommendation
First key recommendation: For the diagnosis of FAS the following abnormalities in *all four diagnostic fields* should be present: 1. Growth deficits 2. Facial characteristics 3. Abnormalities of the central nervous system (CNS) 4. Confirmed or unconfirmed intrauterine alcohol exposure	Expert consensus	
Second key recommendation: For the diagnostic field "*Growth deficits*" at least one of the following abnormalities, adapted to gestational age, age and gender, documented at any time, should be present: 1. Birth weight or body weight ≤ 10th percentile 2. Birth length or body length ≤ 10th percentile 3. Body mass index ≤ 10th percentile	2	A Strong consensus
Third key recommendation: For the diagnostic field "*Facial characteristics*" the following three facial abnormalities should be present simultaneously and may be present at any age: 1. Short palpebral fissure length (≤3rd percentile) 2. Smooth philtrum (Rank 4 or 5 Lip-Philtrum-Guide) 3. Thin upper lip (Rank 4 or 5 Lip-Philtrum-Guide)	1	A Strong consensus
Fourth key recommendation: For the diagnostic field "*Abnormalities of the central nervous system*" (CNS) at least one of the following criteria should be found: 1. Functional abnormalities of the CNS 2. Structural abnormalities of the CNS	Expert consensus	
Fifth key recommendation: For the criteria "*Functional CNS abnormalities*" at least one of the following deficits, that is not adequate for age and that cannot be explained solely by the familial background or social environment should be found: 1. Global intellectual deficit at least two standard deviations below the mean or significant combined developmental delay of children under the age of two years (if measurable by a standardized test at least two standard deviations below the mean). 2. Performance at least two standard deviations below the mean in at least three of the following domains or in at least two of the following domains combined with epilepsy: Language/speech; Fine motor functions; Spatial-visual perception or spatial-constructive skills; Learning or memory skills; Executive functions; Arithmetic skills; Attention; Social skills and behavior	2–4	B Consensus
Sixth key recommendation: For the criteria "*Structural CNS abnormalities*" the following anomaly adapted to gestational age, age and gender, documented at any time, should be found: Microcephaly ≤ 10th percentile/≤3rd percentile	2	B Strong consensus
Seventh key recommendation: if there are abnormalities in the three other diagnostic fields the diagnosis of FAS should be made even when confirmation of maternal alcohol consumption during pregnancy is lacking.	3	A Consensus

All recommendations, except for the cut-off percentile of the head circumference for the children and adolescents with FAS, were adopted with "strong consensus" (agreement by >95% of the participants) or "consensus" (agreement by >75% of the participants).

3.1. *Background information on the first key recommendation: diagnostic fields of FAS*

The diagnosis of FAS in childhood is very important because early diagnosis is a prerequisite for conceptualization, early support and treatment of the patient and thus for a better outcome regarding independent living and working life in adulthood.[1]

Only the FAS facial phenotype is acceptable as screening method for FAS.[2] Criteria in all other diagnostic fields are not specific for patients with FAS.

The diagnostic criteria of FAS are difficult to apply to newborns. The facial features and growth impairments attenuate with age for some patients. Alternatively, the neuropsychiatric manifestations of FAS increase with age meaning that the severity of symptoms tends to increase as does the number of comorbid conditions.

Any professional working in the health or social care system for children who finds abnormalities in one of the

diagnostic fields should proceed to assess the other three diagnostic fields or refer their assessment to other professionals with appropriate qualifications (expert consensus).

Professionals including nurses, midwives, social education workers, physio-, speech- and occupational therapists, psychologists, psychotherapists, physicians in gynecology and obstetrics, pediatricians including neonatology, intensive care, pediatric neurology, developmental medicine, child and adolescent psychiatry, general medicine and public health services should be sensitized for the clinical appearances of FAS and should be encouraged to communicate any reasonable suspicion of FAS and to initiate the necessary diagnostic process.

The content of these recommendations is not to be taken for granted as most of the individuals with FAS in Germany are undiagnosed.

The diagnosis of FAS should involve at least a medical doctor and a psychologist. Where very young children are concerned the evaluation should involve a developmental neurologist. A multimodal and interdisciplinary assessment of the child suspected of FAS is strongly recommended (expert consensus).

3.2. *Background information on the second key recommendation: growth deficits*

Klug et al.[3] found that children with FAS have a significantly lower weight and length at birth or in childhood when compared to children without FAS. They also showed that 22% of the children with FAS had a body mass index below the 3rd percentile in comparison with 3% of the children without FAS (LoE 2c). Day et al.[4] reported in 2011 that 14-year-old children whose mothers drank alcohol during the first and second trimester of pregnancy had a reduced body weight and those whose mothers consumed alcohol in the first trimester had a diminished body length (LoE 2b). The recommendations of the guideline group regarding abnormalities of growth are predominantly based on these two studies.

Growth deficiencies which can be explained solely by familial small body length, constitutional growth retardation, prenatal nutritional deficiencies, skeletal dysplasia, hormonal dysfunctions, genetic syndromes, chronic diseases, malabsorption, malnutrition or neglect should be excluded (expert consensus).

3.3. *Background information on the third key recommendation: facial characteristics*

The FAS-specific facial features sometimes become less distinctive in adolescents or young adults. If the three specific facial characteristics of FAS can be found on photos of these patients at younger age the criteria for “facial characteristics” are fulfilled even if these patients don’t show the specific features at older age (expert consensus).

Already in 1976 Jones et al.[5] reported that children who suffer from intrauterine alcohol exposure have typical facial characteristics. This was confirmed in 1987 in a case–control-study (LoE 4) by Clarren et al.[6] Based on a validation cohort study (LoE 1) Astley and Clarren[2] could show in 1995 that FAS is associated with a specific combination of facial features. This study with direct measurements on the patient’s face shows that independent of ethnicity (Caucasian, African and Asian) and gender the best discriminating features for FAS are a short palpebral fissure length, a smooth philtrum and a thin upper lip. The facial screening used by Astley and Clarren in their study had a sensitivity of 100% and a specificity of 89.4%. Using a computerized measurement of facial photos[7] the screening for FAS with the combination of the three facial characteristics smooth philtrum, thin upper lip and short palpebral fissures (see Fig. 2) reached a positive predictive value of 85.7%, a sensitivity of 100% and a specificity of 99.8%.

The screening via 3D-laser scanner did not improve diagnostic certainty for children with FAS (Ref.[8] LoE 2, Ref.[9] LoE 2).

For a quantitative assessment of the upper lip and the philtrum, Astley and Clarren[10,11] developed a lip-philtrum guide with five facial photos that correspond to a five-point Lickert scale. Measurements of four or five points on this scale show FAS-typical pathological grades for the philtrum and upper lip (see Fig. 2).

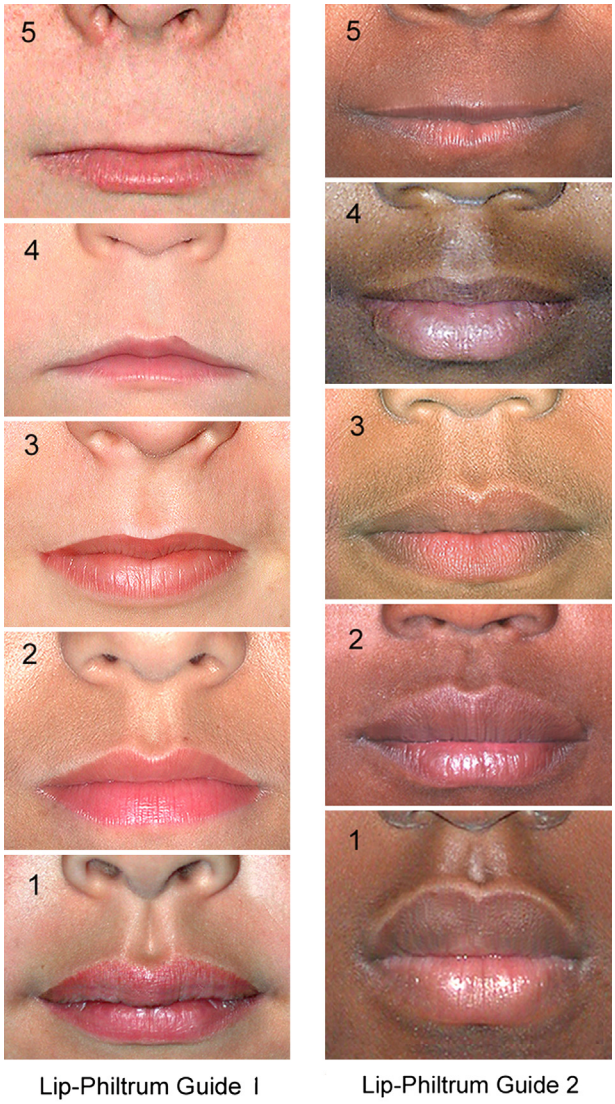

Fig. 2 – Lip-Philtrum Guide (© 2013 Susan Astley PhD, University of Washington).

A self-adhesive dot (e.g. 1 cm in diameter) on the forehead of the patient can be used as a reference point on photos to measure the palpebral fissure length (see Fig. 3). Astley and Kinzel developed a computer program to measure the palpebral fissure length on photos (Fetal Alcohol Syndrome Facial Photographic Analysis Software, Version 2.0.0. Seattle (WA): University of Washington; http://depts.washington.edu/fasdpn/htmls/face-software.htm). Another possibility to measure the palpebral fissure is the direct measurement on the patient with a transparent ruler. It has to be taken into account that sometimes the measurements from pictures differ from those of living patients. The measurement of palpebral fissure length is complex. When one examines the normative charts of this feature it becomes clear that at some ages a 1 mm difference can change the child's percentile rank by over 8 percentile ranks.

Clarren et al.[12] recently developed percentiles for the palpebral fissure length based on measurements of the palpebral fissures of 2097 healthy Canadian girls and boys from 6 to 16 years of age (2010, LoE 2b). In 2011 Astley et al.[13] confirmed in a validation study for the Canadian palpebral fissure length percentiles that the palpebral fissure lengths of healthy American children of Caucasian and Asian ethnicity ($n = 90$) were within the mean of the Canadian percentiles and that American children with FAS ($n = 22$) had palpebral fissure lengths at least two standard deviations below the Canadian mean (LoE 2b-). The Canadian percentiles do not fit for children with African ethnicity.

Percentiles for the palpebral fissure length according to Thomas et al.[14] and Hall et al.[15] gave standard values for children from birth on but probably overestimate the palpebral fissure lengths in the normal population.[13]

For children under the age of six years, percentiles by Strömland et al.[16] can be used.

The German guideline group suggests the use of the Canadian palpebral fissure length percentiles for German children aged 6–16 years with suspected FAS (LoE 2b- → Recommendation Grade B) and the measurement of the upper lip and philtrum with the Lip-Philtrum Guide for children of any age (LoE 1b- → Recommendation Grade A).

3.4. *Background information on the fourth key recommendation: abnormalities of the central nervous system*

The toxic brain damage can primarily manifest as pathological growth of the brain and therefore of the scull (percentile of the head circumference). The damage can also be shown in micro- or macrostructural abnormalities of the brain. These are described in several recent studies that currently however don't reach consistent sufficient evidence.

In everyday life the affected children and adolescents impress with multiple significant functional CNS abnormalities that result from the toxic damage. The clinical and behavioral phenotype with deficits in functional CNS domains can be determined by neurological and neuropsychological assessments.

3.5. *Background information on the fifth key recommendation: functional CNS abnormalities*

The determination of the affected functional brain domains is based on the studies shown in ePub: Table 4.

Most of these studies concerning functional CNS abnormalities in children with FAS are explorative case–control-studies that reach a low level of evidence of 4. Because of small case numbers, lack of blinding of the assessors, no adjustment for multiple testing, no validation on independent collectives, and inadequate consideration of confounders, incidental results cannot be ruled out. The study of Nash et al.[17] regarding attention, social skills and behavior has a better level of evidence of 3. The publication of Coles et al.[18] also evaluates the functional domain "attention" and reaches an LoE of 3. Both studies assess the differentiation between children with FAS and children with attention-deficit-syndrome. The background is that children with FAS are often incorrectly diagnosed only with attention-deficit-syndrome while the underlying alcohol toxic brain damage remains unrecognized.

Adaptive behavior may be one of the most important measures across the age span, especially for older children with IQ above 70.

In summary, no specific neuropsychological profile of children with FAS can be defined because of methodological weaknesses of the available studies.

Therefore, the guideline group gives additional consensus-based recommendations for functional CNS-diagnosis: it is emphasized that functional CNS abnormalities should be assessed with standardized neuropsychological tests or instruments and a psychological or medical evaluation of behavior for the diagnosis of FAS in children and adolescents (expert consensus).

Clear identification of deficits in each of the functional CNS subdomains is essential not only for the diagnosis of FAS but also in order to provide appropriate individual support and training aimed to improve the level of functioning in everyday life and the quality of life of the affected children and their families. Therefore, a sophisticated and complex psychological assessment has a very important role in the diagnostic process for FAS.

For very young patients up to toddler age it is difficult if not impossible to determine functional deficits in subdomains.

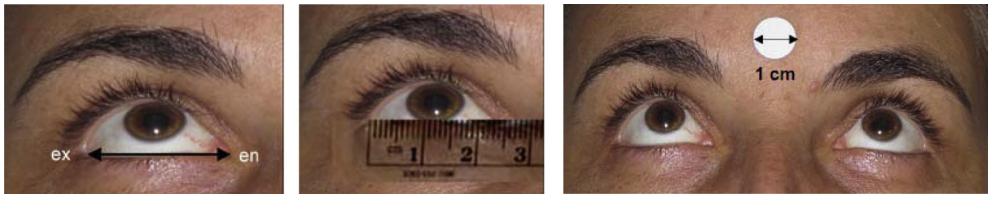

Fig. 3 – Measurement of the palpebral fissure length (Copyright Mirjam Landgraf, University of Munich).

Functional CNS abnormality in patients of this age group mostly consists of developmental delay and therefore requires examination by an experienced developmental neurologist (expert consensus). The inclusion of a standardized developmental test in the diagnostic process is preferable.

Because the alcohol-induced damage of the brain may be either general or multifocal, the patient should show deficits in at least three domains to establish the diagnosis of FAS (expert consensus).

Bell et al.[19] showed in their study of 2010, that 11.8% of children and adults with FASD ($n = 425$) had one or more episodes of seizures and 5.9% suffered from epilepsy (LoE 2). In 2010 Astley[20] examined 1400 individuals with confirmed prenatal alcohol exposure and found a prevalence of seizures among the subset of patients with FAS of 6.5% (10/154). Although there were no control groups in these studies these prevalences for epileptic activity are considerably higher than in the normal population (prevalence of epilepsy ca. 0.4–0.8%[21]). Therefore, for the diagnosis of FAS, epilepsy combined with deficits in two neuropsychological domains fulfils the criteria "Functional CNS abnormalities" (LoE 2 → Recommendation Grade B).

3.6. *Background information on the sixth key recommendation: structural CNS abnormalities*

Day et al.[4] showed in their study ($n = 565$) in 2002 that the head circumferences of children whose mothers consumed alcohol during pregnancy (first trimester 64.6%, second trimester 31.9%, third trimester 75.5%) was significantly smaller than those of the children without intrauterine alcohol exposure (LoE 2). The absolute difference at the age of 14 years was 6.6 mm. Confounders were maternal body length, race, gender, nicotine use, hospital stays and number of siblings. In 2006 Handmaker et al.[22] found in prenatal ultrasound examinations ($n = 167$) that, compared with fetuses of mothers who stopped drinking alcohol after pregnancy recognition, fetuses whose mothers did not stop (52.1%) had no smaller head circumference in absolute terms but a smaller ratio of head circumferences to abdominal circumference (LoE 2).

In the international literature of the last 10 years there is no agreement on the cut-off percentile of the head circumference required for the diagnosis of FAS. The German guideline group could not reach consensus about this criterion either. Therefore, for the diagnosis of FAS, the 3rd as well as the 10th percentile as cut-off for microcephaly were accepted as a criterion for "Structural CNS abnormalities".

Because of the rather poor evidence and the lack of validity criteria of the existing, mostly magnet resonance imaging, studies about structural CNS abnormalities (e.g. volume reductions of the grey and white matter of the cerebrum and cerebellum, caudate nucleus, putamen, cingular gyrus and cerebrospinal fluid, as well as an increased thickness of the cortex: e.g. Refs.[23–28] LoE 4), the guideline group concluded that for the time being structural CNS abnormalities other than microcephaly cannot be accepted as criteria for the diagnosis of FAS in children and adolescents.

3.7. *Background information on the seventh key recommendation: importance of confirmation of maternal alcohol consumption during pregnancy*

In 2010 Burd et al.[29] examined in a retrospective cohort study (LoE 3b) how important confirmed maternal alcohol consumption is for correctly diagnosing FAS. The results show that if alcohol use during pregnancy could not be confirmed, FAS was diagnosed with a higher sensitivity (89% non-confirmed versus 85% confirmed alcohol use) and a lower specificity (71.1% versus 82.4%). Thus, compared with confirmed maternal alcohol use, there is a lower number of false negative and a slightly greater number of false positive diagnoses. Because the guideline group felt that to date a great number of children with FAS in Germany remains unrecognized the guideline group accepted the lower specificity of the diagnostic criterion "non-confirmed alcohol consumption" and concluded that the confirmation of maternal alcohol consumption is not essential for the diagnosis of FAS when all other diagnostic criteria, especially the FAS facial phenotype, are present.

4. Discussion

Many professionals in the German health system, even physicians and psychologists, never heard systematically of FAS in their professional training and have no structured diagnostic pathway available. Therefore they often fail to take the possibility of FAS into consideration when assessing children with developmental disorders. In Germany a considerable number of FAS cases remain unrecognized even though the patients do show multiple signs and symptoms typical for FAS. As a result, those patients and families are missing out on adequate support and specific training.

The *first aim* of the German guideline group was to objectively identify evidence-based diagnostic criteria for children and adolescents with FAS which are presented in this article.

It is difficult to set up studies for the diagnosis of FAS that are well designed and of high methodological quality.

One reason is that such studies rely on subjective information on alcohol use obtained from the mothers rather than on objective measures. This information may be influenced by social desirability bias and recall bias when the pregnancy dates back a longer time. But even objective values in the maternal blood such as carbohydrate-deficient transferrin or gamma-glutamyl transferase may fail to detect alcohol use in early pregnancy when the mother is abstinent in the last months of pregnancy. Future research will show if measurement of fatty acid ethyl esters and ethyl glucuronide in meconium is able to quantify the exposure to ethanol during pregnancy.[30]

In the literature the diagnostic criteria of FAS are often validated in children who already have been diagnosed with FAS earlier. Thus there is no independent reliable reference standard and a risk of incorporation bias. The earlier diagnosis of FAS is based on various diagnostic instruments (e.g. IOM criteria or 4-digit-diagnostic code) with different diagnostic criteria and cut-offs (percentile of head circumference, number of facial anomalies, consideration of functional abnormalities of the central nervous system) and therefore does not

provide the same level of diagnostic discrimination for each patient and for each study.

Despite these methodological limitations, the German guideline group determined explicit diagnostic criteria for FAS in children and adolescents based on the evidence assessed literature of the last 10 years and the consensus of the multidisciplinary guideline group.

As the evidence levels of the publications used for our guideline recommendations are partly still low we must continue to be very circumspect in making a diagnosis of FAS until such time that there is sufficiently robust research work to support it.

FAS must be diagnosed with the highest level of medical and ethical responsibility.

One reason is that the assessment of alcohol consumption during pregnancy remains difficult. On the one hand, many physicians or other medical professionals hesitate asking the mothers about alcohol use because any such question may upset the mother's trust to the point of breaking off contact. On the other hand, many mothers may not truthfully answer such questions because they fear that admitting their true drinking habits may socially stigmatize them. Since many of the children with FAS in Germany live in adoptive or foster families the history of the biological parents is often rudimentary. Therefore the guideline group consented that the confirmation of maternal alcohol use is not a prerequisite for the diagnosis of FAS especially when highly sensitive facial features are present.

Another reason for difficulties in diagnosing FAS is that some characteristics of the affected patients may change with increasing age. The facial features and the growth deficits are typically found in childhood, but can be less prominent in adolescence or adulthood. In early childhood patients with FAS often show only few or no functional CNS abnormalities. By contrast, most of the adolescents with FAS have deficits in behavior, attention and executive functions. Therefore the diagnosis of FAS depends on an experienced developmental assessment in very early childhood and on a complex neuropsychological assessment during later childhood, adolescence and adulthood. For evaluation of the functional CNS abnormalities, neuropsychological tests and instruments were evaluated regarding quality criteria (standardization, reliability and validity) and adequate psychological instruments were proposed for the assessment of each typically affected neuropsychological subdomain in children and adolescents with FAS in Germany.

The *second aim* of the guideline group was to improve awareness and knowledge among health professionals about the typical characteristics and deficits of children and adolescents with FAS. Evidence based knowledge about the diagnosis of fetal alcohol syndrome should be as ubiquitous as the use of this drug is in our alcohol permissive societies.

At present the diagnostic capacity available in Germany is not adequate to meet the needs for diagnosis of FAS. Attention to FASD in the training programs in Germany (Pediatrics, Neuropediatrics, Neurology, Psychiatry, Psychology, Social Workers, etc.) should be increased to be sure that appropriate staffing requirements for diagnosis of FAS can be achieved.

Effective education of the German society about the lifelong negative consequences of maternal alcohol consumption during pregnancy can only succeed with the help of

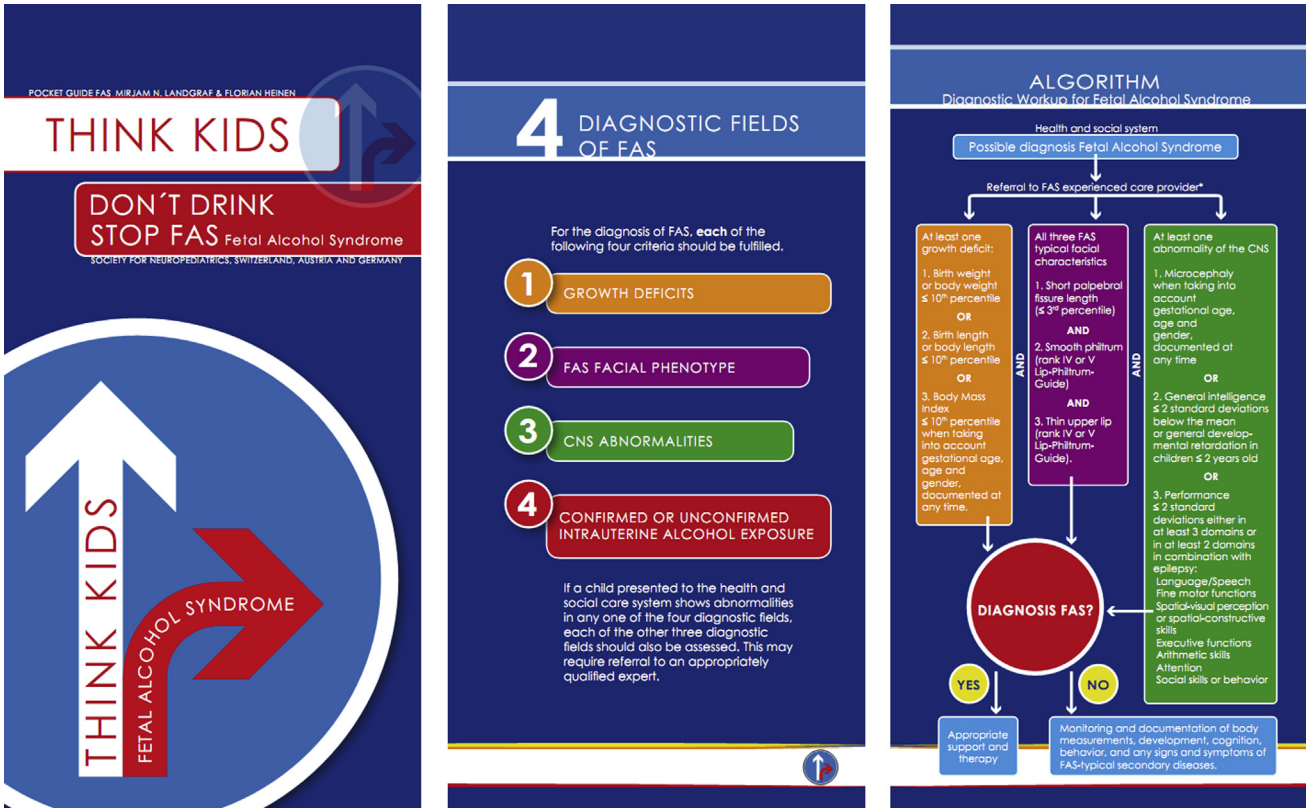

Fig. 4 – Pocket Guide FAS (example pages).

adequately sensitized and experienced professionals in the health and social system.

For *practical clinical use* of the diagnostic criteria the following material was developed:

Pocket Guide FAS: an algorithm shows the diagnostic process of children with suspected FAS at a glance. For each of the four diagnostic fields differential diagnosis is listed. The Pocket Guide also includes web-links for further information regarding prevention of alcohol use during pregnancy and support for affected families. Example pages are depicted in Fig. 4. The Pocket Guide FAS can be downloaded as ePub.

Due to the limited available evidence these guideline recommendations are restricted to the full clinical picture of fetal alcohol syndrome in children and adolescents.

The guideline group is fully aware of the fact that the other fetal alcohol spectrum disorders (FASD), which have an estimated ten times higher prevalence than FAS, are currently excluded. As the diagnosis of FASD is much more difficult because the affected patients may have a quite normal physical appearance, and as these patients often do have the same problems in everyday life as do patients with FAS, further research is needed.

Another limitation of our guideline is that it only addresses the diagnosis of FAS and does not propose any recommendations for the adequate treatment of patients with FAS.

Defining the diagnostic approach to FAS is only seen as a first but necessary step to avoid developmental misconceptions caused by neglecting alcohol as an irreversible toxic determiner of development. The German guideline is only tackling the tip of the iceberg.

The development of evidence-based guidelines for the treatment and support of affected children and their families is urgently needed.

Furthermore, the far-reaching negative consequences of intrauterine alcohol exposure in adult life including the inability to live and work independently should also be given attention in future research and guidelines.

Other points for future consideration in German research are adequate methods to screen for prenatal alcohol exposure in prenatal care and substance abuse treatment programs and to screen for FAS in schools, pediatric clinics, clinics for developmental medicine, special education programs, foster care programs and in Juvenile Justice programs.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejpn.2013.03.008.

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