European Journal of Medical Genetics 60 (2017) 49–54

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: http://www.elsevier.com/locate/ejmg

Neurodevelopmental disorder associated with prenatal exposure to alcohol (ND-PAE): A proposed diagnostic method of capturing the neurocognitive phenotype of FASD

Julie A. Kable [a, b, *], Raja A.S. Mukherjee [c]

[a] Department of Psychiatry and Behavioral Science, Emory University School of Medicine, Atlanta, GA, 30324, USA
[b] Department of Pediatrics Emory, University School of Medicine, Atlanta, GA, 30324, USA
[c] Lead Clinician FASD Specialist Behavior Clinic, Surrey and Borders Partnership NHS Foundation Trust, 116-118 Station Rd East, Oxted, Surrey, RH80QA, UK

ARTICLE INFO

Article history:
Received 26 January 2016
Accepted 12 September 2016
Available online 13 September 2016

Keywords:
Fetal alcohol spectrum disorders
ND-PAE
Psychiatric diagnosis
Mental health

ABSTRACT

Neurobehavioral Disorder associated with Prenatal Alcohol Exposure (ND-PAE) was proposed as a diagnostic formulation intended to capture the range of mental health problems occurring in alcohol-affected individuals with a history of prenatal alcohol exposure. The proposed criteria for the disorder are reviewed as well as various factors considered in the development of the disorder and its associated criteria. The taxonomic research related to the disorder is reviewed with preliminary analyses indicating that clinicians are readily able to agree when applying the diagnostic criteria but that the adaptive functioning criteria may need to be modified to expand its coverage of alcohol-affected individuals and to aid in discriminating these individuals from others not alcohol-affected. Finally, the challenges with translating the diagnosis into European medical and mental healthcare systems are discussed and recommendations for facilitating implementation are made.

1. Introduction

The identification of the neurobehavioral consequences of prenatal alcohol exposure (PAE) has proven to be multi-faceted and complex. Although considerable research has been done documenting a variety of neurocognitive and behavioral outcomes (see reviews (Senturias, 2014; Riley et al., 2011)), a consistent diagnostic formulation of these symptoms is complicated by the variability in the consumption patterns of women who drink in pregnancy (Halmesmaki et al., 1987; Iversen et al., 2015; Fortin et al., 2016), maternal nutrition (Keen et al., 2010), the metabolism of the mother (Church et al., 1990), the genetics and epigenetics of the mother and child (Mead and Sarkar, 2014; Sulik, 2014; Gilliam and Irtenkauf, 1990; Israel et al., 2006), and the impact of the postnatal environment on these outcomes (May and Gossage, 2011). Various diagnostic systems for fetal alcohol spectrum disorders ((Astley, 2013; Hoyme et al., 2005; Stratton et al., 1996; Astley, 2006) have attempted to formulate methods of identifying alcohol-affected individuals for appropriate diagnosis and to facilitate their access to treatment services but there is a lack of consistency across these systems (Astley, 2006; Coles. et al., 2016). In addition, these systems do not directly map onto a unique recognized mental health diagnosis making it difficult to identify individuals who are alcohol-affected within existing mental health care systems, which can aid in identifying the scope of the problem and help with allocating appropriate resources for care (Sanders, 2013). Neurobehavioral Disorder Associated with Prenatal Alcohol Exposure (ND-PAE) (Kable et al., 2014) was developed to fill this gap in the identification and treatment of the behavioral and mental health problems of individuals affected by prenatal alcohol exposure (PAE). The disorder was included in the most recent revision of the American Psychiatric Association Diagnostic and Statistical Manual, 5th edition under the Conditions for Further Study section (American Psychiatric Association, 2013). While additional research is being

Abbreviations: AF 2 of 4, Adaptive functioning criteria of the DSM5 that requires two symptoms of four proposed systems; ARND, Alcohol-related neurodevelopmental disorder; DSM5, American Psychiatric Association Diagnostic and Statistical Manual, 5th edition; FAS, Fetal alcohol syndrome; FASD, Fetal alcohol spectrum disorder; ICD, International Classification of Diseases; MDT, Multidisciplinary Team; ND-PAE, Neurodevelopmental Disorder associated with Prenatal Alcohol Exposure; PAE, Prenatal alcohol exposure; pFAS, partial Fetal alcohol syndrome; UK, United Kingdom.

* Corresponding author. 12 Executive Park, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA 30329, USA.
E-mail address: jkabl01@emory.edu (J.A. Kable).

http://dx.doi.org/10.1016/j.ejmg.2016.09.013
1769-7212/

done to validate the proposed criteria for the disorder, clinics worldwide have initiated using the diagnosis.

2. The DSM5 definition of ND-PAE

The Diagnostic and Statistical Manual, 5th edition (DSM; (American Psychiatric Association, 2013)) is an official publication of the American Psychiatric Association and is used as a standard reference for clinical diagnosis and practice in the field of mental health both in America and throughout many parts of the world. In addition to psychiatrists, the manual is used by a variety of mental health professionals, including other medical providers (i.e. neurologists, developmental pediatricians, and geneticists), psychologists, nurse practitioners, social workers, counselors, and addiction specialists. Although the DSM5 has had its criticisms (Insel, 2014), the document is used to define psychiatric disorders for both clinical research and practice by these various professionals and the criteria used for identification of the neurobehavioral consequences of PAE had to be formulated within a framework that could be used by these various mental health professionals. This is in stark contrast to traditional FASD diagnostic formulations which were predominantly implemented by geneticists or developmental pediatricians either in independent practice or in the context of multidisciplinary team (MDT) environments. MDT assessments are still viewed as the ideal context for FASD assessments, including making the diagnosis of ND-PAE (Carmichael Olson, 2015) but there is an increasing awareness that such contexts cannot meet the need relative to the estimates of the prevalence of alcohol-affected individuals (May et al., 2014).

PAE is associated with a broad spectrum of neurobehavioral impact, which was consolidated into three domains of functioning that were proposed as being critical to identifying those affected by PAE and in need of mental health services. The three designated domains proposed as criteria for the disorder are as follows: (1) neurocognitive, (2) self-regulation and (3) adaptive functioning. The neurocognitive domain includes five potential symptoms including impairments in global intellectual functioning, executive functioning, learning, memory, or visual-spatial reasoning and the self-regulation domain includes three possible symptoms, including impairment in mood or behavioral regulation, attention deficits, or impairment in impulse control. Only one symptom needs to be endorsed within the neurocognitive and self-regulation domains but the adaptive domain requires two of four symptoms (impairments in communication, social, daily living skills, or motor functioning) needed for endorsement of the domain of which endorsement of either communication or social impairments is needed (AF 2 of 4 criteria). As proposed, ND-PAE can be diagnosed either in the presence or absence of the physical effects of PAE (i.e., a diagnosis of Fetal Alcohol Syndrome (FAS) or partial FAS (pFAS)), making it distinctly different from previous conceptualizations of alcohol-related neurodevelopmental disorder (ARND).

To meet criteria for ND-PAE, the neurobehavioral problems have to cause clinically significant levels of impairment in social, academic, occupational, or other areas of functioning, which is a standard threshold utilized in mental health diagnostic criteria. In addition, the symptoms cannot be explained by substance use, environmental neglect or by other medical conditions, including head trauma or other genetic disorders.

3. Why a mental health diagnosis is needed?

Mental health providers who are working with individuals with a history of PAE have struggled with appropriately capturing their patient's symptoms using the previously existing psychiatric diagnostic categories. Often individuals seen in clinics were given multiple diagnostic codes to document the range of impact on everyday functioning. Providers were often dissatisfied as those who were alcohol-affected often did not benefit from the same intervention approaches associated with a given diagnosis (Kable et al., 2016). In addition, the lack of a specific mental health diagnostic code to capture the impact of PAE on the developing brain meant that the scope of the public health need was not being adequately documented as there was no way to differentiate alcohol-affected individuals with a given diagnosis (i.e. ADHD, Combined) from those without a PAE history. Furthermore, the development of targeted interventions that focused in repairing alcohol-specific brain damage was hampered by the lack of specificity in the diagnostic formulation. Finally, the development of a specific mental health diagnosis for alcohol-affected individuals also aids in families being able to more readily access diagnostic assessments and habilitative care services as previously, the only formal recognized diagnostic codes that could be used for coding and billing purposes within many mental health care systems were medical disorders described by the International Classification of Diseases (ICD) of the World Health Organization (World Health Organization, 2011) and were limited to those who had facial dysmorphia and growth delays. This resulted in reimbursement for mental health care services often being denied and became a barrier to accessing necessary habilitative care services. Alcohol-exposed individuals who did not meet full criteria for FAS, have been found to be at higher risk than those who are diagnosed with FAS/pFAS for a number of adverse life outcomes, including delinquency, school failure, and substance abuse problems (Streissguth et al., 1997). These outcomes are most likely the result of the systemic barriers to accessing habilitative care in the absence of a clear diagnosis. The inclusion of a diagnosis of ND-PAE in the DSM5 facilitates recognition of the treatment needs of individuals negatively impacted by PAE who may or may not have the physical effects of PAE.

4. Why ND-PAE and not ARND?

ARND was originally proposed in the Institute of Medicine's report on FAS (Stratton et al., 1996) but was conceived of as a category for individuals who did not have the physical effects of PAE but did have some of the neurobehavioral characteristics associated with PAE. Although various symptoms were suggested as indicators of the impact of PAE, no formal diagnostic criteria were elaborated. As a result, the various FASD clinical diagnostic schemas attempted to operationalize criteria but a consistent definition of ARND across these systems has not been achieved. In addition, no conceptualization of ARND has been subjected to the criteria needed to formalize a psychiatric diagnosis, which involves examining the psychometric characteristics of the symptoms used to formulate the diagnosis. The existing definitions also could not be reformulated into appropriate DSM5 criteria and a diagnostic terminology was needed to insure that all alcohol-affected individuals would have access to mental health services not just those with or without the physical effects of PAE. ND-PAE was formulated as an alternative to ARND to avoid confusion with these pre-existing diagnostic classification systems and formalized research definitions of ARND.

5. Why were head circumference and neuroimaging evidence omitted from ND-PAE diagnostic criteria?

Although most FASD diagnostic classification systems incorporate head circumference and neuroimaging results into their criteria, ND-PAE does not include these in the diagnostic formulation. This was done because among the diversity of professionals

who utilize the DSM5, many do not conduct physical examinations and do not have the capacity to independently obtain neuroimaging studies. Criteria for DSM5 disorders were required to be behavioral-based symptoms that could be applied to case conceptualizations by all mental health professionals. Although this is somewhat dissatisfying to professionals who are used to using these indices in their FASD case conceptualization, individuals with small head sizes or abnormal MRI findings are unlikely to not have functional neurobehavioral consequences associated with these physical alterations. Those who do not have functional neurobehavioral consequences are not really in need of mental health services and therefore do not warrant being given a mental health diagnosis.

6. The "proposed" vs. active use status of the ND-PAE diagnosis

When the DSM5 was published, ND-PAE was mentioned in two sections with one being in the "Conditions for Further Study" and the other in "Neurodevelopmental Disorders" under the disorder entitled "Other Specified Neurodevelopmental Disorder (315.8/(F88)). This has created some confusion in that disorders under the "Conditions for Further Study" are prohibited from being used in a clinical context but the manual specifically recommends coding the disorder under the "Other Specified Neurodevelopmental Disorder." The latter is a category applied to individuals with neurodevelopmental symptoms that impair functioning but who do not meet criteria for other neurodevelopmental diagnoses (i.e. intellectual deficiency). Although recommended for use to diagnosis individuals with alcohol-related neurobehavioral disabilities, the same category could be used to code a variety of other neurodevelopmental disorders (i.e., a nonverbal learning disability) and is not specific to impact of PAE on the developing brain. Obviously, it would be better to have ND-PAE associated with its own unique diagnostic code to aid in tracking for public health and advocacy purposes but the existing schema has allowed mental health clinicians to begin to apply the diagnosis to their patients. Evidence supporting the presence of the symptoms used in the diagnostic formulation of ND-PAE is already substantial (Kable et al., 2014; Doyle and Mattson, 2015) but additional taxometric research is needed for the condition to be documented more fully as a unique psychiatric disorder.

7. Active studies exploring the psychometric properties of the ND-PAE diagnosis

Basic criteria for evaluating the validity of a psychiatric disorder have been proposed (Blashfield and Draguns, 1976). Assessing the diagnostic coverage and descriptive validity of the symptoms are part of the criteria for evaluating psychiatric disorders. This involves making sure that most or all of the individuals recognized as having a disorder meet the proposed criteria for the disorder. Establishing the homogeneity of the symptoms associated with a given disorder is also a prerequisite step to exploring the disorder's capacity to differentiate affected individuals from other populations. Finally, the relative contribution of each of the proposed symptoms in differentiating those affected by PAE from typically developing individuals and individuals with other mental health or developmental disorders is needed. Several projects are actively pursuing these analyses within existing cohorts to further inform the formulation of the diagnosis. These projects involve an archival clinical sample (Bell, 2014), an extensive database available from participants enrolled in an FASD intervention study (Kable et al., 2007a), and three large cohorts of individuals with a history of PAE (Mattson et al., 2013; May, 2015, Chambers et al., 2015). With the exception of the Bell study, these projects are in their early stages and the results have only been presented at conferences and in published abstracts.

Data on inter-observer agreement using an archival clinical database has been high (Bell, 2014) with 98% agreement reported in a clinical sample of low-income predominantly African American psychiatric patients. Among participants enrolled in a math intervention study who were identified as having FAS or pFAS (Kable et al., 2007b), the percentage of endorsement for neurocognitive and self-regulation symptoms was in the 90s regardless of the threshold adopted (1.5 or 1.0 standard deviation units (SD)) for delineating pathology. Less agreement was found among the adaptive functioning criteria at the 1.5 SD threshold but the agreement was in the 80s for the 1.0 SD threshold (Kable and Coles, 2015). Recommendations were made for modifying the adaptive functioning criteria to include only one symptom rather than the 2 of 4 criteria recommended in the DSM5 to expand the breadth of coverage of alcohol-affected individuals.

Estimates of the homogeneity of symptoms have been high with Cronbach alphas, a measure of internal consistency, ranging in the mid to high 70s (Kable and Coles, 2015) in both a sample of individuals diagnosed with FAS/pFAS who were enrolled in an intervention study (Kable and Coles, 2015) and an epidemiological sample identified as being at risk for ND-PAE based on their mother's report of drinking or their own physical characteristics (Kable, 2015).

The discriminate validity of the symptoms in differentiating typically developing individuals has been explored in a sample of individuals enrolled in the large multi-site project attempting to distinguish the unique neurobehavioral profile of alcohol-affected individuals from typically developing individuals and from various contrast groups, including those with ADHD, various behavioral problems, and developmental problems (Mattson et al., 2013). Using area under the curve analysis to assess the symptom's discriminate validity relative to a diverse contrast group comprised of typically developing individuals and those with ADHD, estimates ranged from the poor (mid 60s) to high (low 80s) depending on the threshold used for endorsing symptoms and whether 1 or 2 adaptive functioning symptoms were required. Modifications of the adaptive functioning criteria were also recommended in this study to improve the discriminative validity of the symptoms (Mattson et al., 2015).

8. The minimal levels of prenatal alcohol-exposure requirement

In order to consider a ND-PAE diagnosis, a confirmed history of "more than minimal" levels of alcohol exposure is needed during gestation. This information can be collected from maternal report of alcohol use in pregnancy, medical or other records, or by clinical observation. "More than minimal" is further defined as being greater than 13 drinks per month during pregnancy and no more than 2 drinks on any one occasion. This criteria has been controversial but was not intended to imply that drinking less than the defined minimal level was in any way safe or non-deleterious to the fetus (Kable et al., 2016). The threshold was chosen to establish a minimum level so that the diagnosis was not over-used as the base rate of drinking any alcohol among women of child-bearing years is relatively high (Tan et al., 2015) and the impact of low levels of drinking has been controversial (Reynolds et al., 2015). Establishing a threshold of exposure level that produces clinically significant levels of impairment is a daunting task based on the variability of symptoms seen in offspring of women who drink during pregnancy (Abel, 1996; Reynolds et al., 2015). The use of prospective longitudinal studies of PAE may be needed to further inform the diagnostic

criteria regarding what changes should be made in specifying the "more than minimal" level of PAE needed for a diagnosis.

9. European experience with ND-PAE

The DSM5 proposed diagnostic criteria for NDPAE has had unclear and uncertain uptake in Europe. ICD (World Health Organization, 2011) has tended to have a greater precedence of use, in terms of recording diagnostic outcome, especially in the UK. DSM does however have situations where it is used more. A good example is with regards to ADHD. The defined criteria have been used, for example to develop the Diagnostic Interview for ADHD in Adults (DIVA; (Kooij, 2013)) as a diagnostic framework in adult ADHD clinics where ICD is used far less.

FAS, but more importantly the wider spectrum of presentation, has tended to be diagnosed primarily in specialist clinics throughout Europe. Whilst the more recognized part of the syndrome (FAS) has been seen in clinical genetics (dysmorphology), pediatric services as well as some child psychiatry services, evidence would suggest that the level of knowledge in various countries around Europe with regards to this wider spectrum is limited. For example, a recent study completed in the UK highlighted that whilst many clinicians had heard about FAS, many were unprepared regarding how to apply the diagnostic criterion and what parameters to measure. Further, the fact that many individuals did not have full facial characteristics left them uncertain both about what to do, but also where to get help. Of those professionals who responded, 60% of the total group and 72% of pediatricians reported the label as stigmatizing (Mukherjee et al., 2015).

What is increasingly evident from other literature is that even in genetic syndromes, environmental factors may have a role in influencing outcomes via epigenetic mechanisms (Millan, 2013). Alcohol is a compound known to exert an epigenetic effect in and of itself (Haycock, 2009). For example prenatal alcohol has been shown to modify the retrotransposon methylation level prior to the A^{vy} gene in an *agouti* mouse model leading hair coloration patterns to vary (Haycock, 2009).

Across Europe the use of the recognized diagnostic approaches for FASD varies, with some clinics tending to favor the University of Seattle's four digit approach (Astley and Clarren, 2000) whilst others for example, many places in the UK, follow the instructions found in the 2005 Canadian consensus guidance (Chudley et al., 2005). All approaches, however, highlight the need for a multidisciplinary team (MDT) approach, or at least a multimodal assessment looking at multiple cognitive and functional domains. Unfortunately for many clinicians, they work as individual practitioners and do not easily have access to the wider MDT.

Whilst the development of linked clinics, working in a hub and spoke model of service delivery, with regional specialist centers supporting the local practitioner, may resolve this issue (Mukherjee, 2014), it is a model that is not established widely in Europe. Application therefore of the NDPAE diagnosis is seemingly easiest for those clinics where that multidisciplinary approach is already established. Where the different parameters required for a diagnosis cannot be assessed in full, the application of the DSM criteria will be challenging. Developing assessment tools with sufficient validity and sensitivity to meet the different DSM criterion levels has yet to be achieved for different levels on the service delivery ladder. Bearing in mind also the cultural and language differences, applying the tools from an English speaking country does not easily translate to non-English speaking areas.

Tables 1–3 below highlights 2014 audit findings from the UK National FASD clinic (www.fasdclinic.com). As a specialist multidisciplinary service, it is limited in assessment capacity by resource allocation. This audit highlights the first five years of its function and growth. 82 cases were seen in that first period of time. The clinic process and description can be found in other previously published articles (Mukherjee et al., 2006, 2011). Table 1 highlights the breakdown of demographic background showing an average age of eleven years seven months with the majority of those seen in the borderline intellectual range. A 60/40 split of male to female was seen. Table 2 highlights the breakdown of scores achieved when applied to the four digit criterion as described in the Canadian guidance (Chudley et al., 2005). More recent re-evaluation of those 82 cases applying the new criterion from DSM5 are shown in Table 3. When applied to diagnostic criterion it demonstrates the range of diagnoses that were seen but also that NDPAE relates more easily to an Alcohol-Related Neurodevelopmental Disorder diagnosis from the IOM criterion or four digit diagnostic category of E and F. The lack of confirmed alcohol history was one common reason for criteria not being met. Because the National clinic is a complex needs multidisciplinary team, application and identification of the wider cognitive criteria is easy to make across all ages. It is unclear if this would have translated so well where a MDT approach was not available.

Table 1
Demographic breakdown from Jan 2014 clinic audit (82 cases seen).

	Classification	Number	%
Age	<10	37	45.1
(3.4–26.3 Range)	10–14	29	35.4
(mean 11.7)	15–19	10	12.2
	20+	6	7.3
Gender	Male	49	59.8
	Female	33	40.2
IQ level	Normal Range	29	35.4
(ICD10 defined)	Borderline	42	51.2
	Mild ID	10	12.2
	Moderate ID	1	1.2

The diagnosis of FASD is also one of inclusion of the identifiable classic symptoms but also importantly, it is important to exclude as far as possible other factors. This is particularly highlighted in the DSM5 criteria. Obtaining a CGH micro-array in the UK is straightforward and has been recommended as the minimum test that should take place to rule out known disorders (Douzgou et al., 2012). As the authors highlight, an important role in all FASD cases for a clinical geneticist, is to rule out other disorders as much as to diagnose the more obvious cases of FAS. As most clinical geneticists are not trained in behaviour assessment this remains a key role for geneticists in developed countries (Douzgou et al., 2012) In less developed European and other international countries. Obtaining a CGH microarray may not be as easy. Thus in the UK ruling out other genetic conditions is less of a factor than elsewhere. In those countries where these tests are not easily available, recognition of the dysmorphology remains more important. Where reliance on the dysmorphology decreases, through access to wider diagnostic technology, greater resource can be directed towards psychological and functional evaluation. Further, when considering our clinic figures over 70% of those attending our clinic did not have facial dysmorphology (Table 2), understanding the impact and then ruling out the influence of these other factors becomes vital. It is

Table 2
4 digit scores breakdown Jan 2014 Audit (82 cases seen) Number meeting criteria (percentage).

	Growth	Face	CNS	Alcohol
1	36 (43.9)	2 (2.4)	1 (1.2)	0 (0)
2	17 (20.7)	57 (69.5)	8 (9.8)	5 (6.1)
3	8 (9.8)	8 (9.8)	54 (65.9)	37 (45.1)
4	21 (25.6)	15 (18.3)	19 (23.2)	40 (48.8)

Table 3
Diagnostic codes met based on descriptions in Chudley et al., 2005 (number [% of total group]) when applied to Jan 2014 audit (total N = 82).

IOM category	IOM number [%]	4 digit category	4 digit: Number [%]	NDPAE criteria met: Number [%]
FAS Alcohol Exposed	10 [12.2]	A	10 [12.2]	10 [12.2]
FAS Alcohol unknown	1 [1.2]	B	1 [1.2]	0
PFAS	10 [12.2]	C	10 [12.2]	10 [12.2]
ARND	52 [64.2]	E/F	52 [63.4]	52 [63.4]
		G/H	7 [8.6]	0
Poss ARND	3 [3.6]	Other	2 [2.4]	0
Not FASD	6 [7.3]			0
Total of full group met a confirmed FASD diagnosis	73 [59.9]	Total of full group met a confirmed FASD diagnosis	73 [89.0]	(72 [87.8])

possible through detailed evaluation to undertake these tasks but once again to do this a full multidisciplinary, multi-professional team is required. Factors such as prematurity and perinatal difficulties are often easier to identify and rule out as a single practitioner. This can be achieved through the taking of a careful history. The impact of other substances, neglect or where the cognitive presentation is not clear cut, may be harder for many health professional working in isolation.

For a diagnostic system designed primarily for the American system this lack of multidisciplinary resource can become a challenge. The application of the criteria may well therefore vary by resource as much as by validity of the criteria.

Different countries across Europe have different approaches to funding and commissioning. Whilst free public health care is provided in some countries, independent insurance and private payments supplements provision in others. Thus the provision and access to services varies across different countries in Europe.

The system in the UK, as an example of service provision, is an established public sector funded healthcare system which has access to many modern techniques and approaches. However, access to specialist centers is often limited through budget restrictions. All levels of care will therefore not be immediately open to everyone. Restrictions on availability of resource will mean that choices have to be made around what provisions are prioritized. At the time where FASD is not widely recognized or accepted (Mukherjee et al., 2015), establishing diagnostic criterion which all parties are able to use is an important step in increasing both recognition but later management and prevention of secondary disabilities.

The inconsistencies in approach and the difficulties establishing an accepted pathway as well as the clear definition in both DSM5 and ICD 10 of the wider spectrum of disorder have left many commissioners stating that it is therefore not necessary to address the issue. To overcome the argument against service development may well require a system wide approach to change, however the recognition of need, partly through accepted criteria for the full spectrum of presentation would often have to precede this change.

This again highlights the importance of establishing a clear agreed approach to diagnosis beyond that where dysmorphology is present. Whilst the evidence and good practice should be established to ensure validity of the diagnosis emphasizing specificity over sensitivity for a clinical setting, it must also be a model that can be applied beyond just the North American continent but can be used and applied by all. This also allows clarification that the symptoms being seen in Europe, Asia and wider afield are those that are seen in clinics in parts of the world where the criteria were first developed.

Declaration of interest

Dr Mukherjee has received honoraria from various groups including pharmaceutical companies for talks on FASD. He is an unpaid medical advisor to various UK FASD charities.

Acknowledgements:

A portion of the time devoted to writing this manuscript was funded with the support the National Institute on Alcohol Abuse and Alcoholism subcontract #10313752 to grant #U01 AA019879-01.

References

Abel, E.L., 1996. Fetal Alcohol Syndrome: from Mechanism to Prevention. CRC Press, Boca Raton, FL.
American Psychiatric Association, 2013. Diagnostic and Statisical Manual of Mental Disorders, Fifth Edition. American Psychiatric Association, Washington, DC.
Astley, S.J., 2006. Comparison of the 4-digit diagnostic code and the Hoyme diagnostic guidelines for fetal alcohol spectrum disorders. Pediatrics 118, 1532–1545.
Astley, S.J., 2013. Validation of the fetal alcohol spectrum disorder (FASD) 4-Digit Diagnostic Code. J. Popul. Ther. Clin. Pharmacol. 20, e416–e467.
Astley, S.J., Clarren, S.K., 2000. Diagnosing the full spectrum of fetal alcohol-exposed individuals: introducing the 4-digit diagnostic code. Alcohol Alcohol 35, 400–410.
Bell, C.C., 2014. Fetal alcohol exposure among African Americans. Psychiatric Serv. 65, 569.
Blashfield, R.K., Draguns, J.G., 1976. Evaluative criteria for psychiatric classification. J. Abnorm Psychol. 85, 140–150.
Carmichael Olson, H., 2015. Advancing recognition of fetal alcohol spectrum disorders: the proposed DSM-5 diagnosis of "neurobehavioral disorder associated with prenatal alcohol exposure (ND-PAE). Curr. Dev. Disord. Rep. 2, 187–198.
Chambers, C.D., Zellner, J.A., Feldman, H., Akshoomoff, N., Xu, R., Coles, C.D., Kable, J.A., Manning, M., Adam, M., Vaux, K., Jones, K.L., 2015. Developing a valid prevalence estimate for fetal alcohol spectrumdisorders in a large, diverse urban U.S. Community. Alcohol. Clin. Exp. Res. 39, 260A.
Chudley, A.E., Conry, J., Cook, J.L., Loock, C., Rosales, T., Leblanc, N., Public Health Agency of Canada's National Advisory Committee on Fetal Alcohol Spectrum, D, 2005. Fetal alcohol spectrum disorder: Canadian guidelines for diagnosis. CMAJ 172, S1–S21.
Church, M.W., Abel, E.L., Dintcheff, B.A., Matyjasik, C., 1990. Maternal age and blood alcohol concentration in the pregnant Long-Evans rat. J. Pharmacol. Exp. Ther. 253, 192–199.
Coles, C.D., Gailey, A., Mulle, J., Kable, J.A., Lynch, M.E., Jones, K.L., 2016. A comparison among five methods for the clinical diagnosis of Fetal Alcohol Spectrum Disorders (FASD). Alcohol. Clin. Exp. Res. 40 (5), 1000–1009.
Douzgou, S., Breen, C., Crow, Y.J., Chandler, K., Metcalfe, K., Jones, E., Kerr, B., Clayton-smith, J., 2012. Diagnosing fetal alcohol syndrome: new insights from newer genetic technologies. Arch. Dis. Child. 97, 812–817.
Doyle, L.R., Mattson, S.N., 2015. Neurobehavioral disorder associated with prenatal alcohol exposure (ND-PAE): review of evidence and guidelines for assessment. Curr. Dev. Disord. Rep. 2, 175–186.
Fortin, M., Muckle, G., Anassour-Laouan-Sidi, E., Jacobson, S.W., Jacobson, J.L., Belanger, R.E., 2016. Trajectories of alcohol use and binge drinking among pregnant inuit women. Alcohol Alcohol. 51 (3), 339–346. http://dx.doi.org/10.1093/alcalc/agv112. PubMed PMID: WOS:000376098900015.
Gilliam, D.M., Irtenkauf, K.T., 1990. Maternal genetic effects on ethanol teratogenesis and dominance of relative embryonic resistance to malformations. Alcohol Clin. Exp. Res. 14, 539–545.
Halmesmaki, E., Raivio, K.O., Ylikorkala, O., 1987. Patterns of alcohol consumption during pregnancy. Obstet. Gynecol. 69, 594–597.
Haycock, P.C., 2009. Fetal alcohol spectrum disorders: the epigenetic perspective. Biol. Reprod. 81, 607–617.
Hoyme, H.E., May, P.A., Kalberg, W.O., Kodituwakku, P., Gossage, J.P., Trujillo, P.M., Buckley, D.G., Miller, J.H., Aragon, A.S., Khaole, N., Viljoen, D.L., Jones, K.L., Robinson, L.K., 2005. A practical clinical approach to diagnosis of fetal alcohol spectrum disorders: clarification of the 1996 institute of medicine criteria. Pediatrics 115, 39–47.
Insel, T.R., 2014. Mental disorders in childhood: shifting the focus from behavioral

symptoms to neurodevelopmental trajectories. JAMA 311, 1727–1728.
Israel, Y., Quintanilla, M.E., Sapag, A., Tampier, L., 2006. Combined effects of aldehyde dehydrogenase variants and maternal mitochondrial genes on alcohol consumption. Alcohol Res. Health 29, 281–285.
Iversen, M.L., Sorensen, N.O., Broberg, L., Damm, P., Hedegaard, M., Tabor, A., Hegaard, H.K., 2015. Alcohol consumption and binge drinking in early pregnancy. A cross-sectional study with data from the Copenhagen Pregnancy Cohort. BMC Pregnancy Childbirth 15, 327.
Kable, J. A. 2015. Update on the empirical evidence supporting the reliability and validity of the Neurobehavioral Disorder associated with Prenatal Alcohol Exposure (ND-PAE) diagnosisa. American Psychiatric Association 168th Annual Meeting. Toronto, Canada.
Kable, J.A., Coles, C.D., 2015. Empirical evidence supporting the internal validity of the ND-PAE diagnosis. (2015). Alcoholism: clinical and Experimental Research 39: xA. Alcohol. Clin. Exp. Res. 39, 226A.
Kable, J.A., Coles, C.D., Taddeo, E., 2007a. Socio-cognitive habilitation using the math interactive learning experience program for alcohol-affected children. Alcoholism-Clinical Exp. Res. 31, 1425–1434.
Kable, J.A., Coles, C.D., Taddeo, E., 2007b. Socio-cognitive habilitation using the math interactive learning experience program for alcohol-affected children. Alcohol Clin. Exp. Res. 31, 1425–1434.
Kable, J.A., O'connor, M.J., Olson, H.C., Paley, B., Mattson, S.N., Anderson, S., Riley, E.P., 2014. Neurobehavioral Disorder Associated with Prenatal Alcohol Exposure: proposed DSM-5 Diagnosis.
Kable, J.A., O'Connor, M.J., Carmichael Olson, H., Paley, B., Mattson, S.N., Anderson, S., Riley, E.P., 2016. Neurobehavioral disorder associated with prenatal alcohol exposure (ND-PAE): proposed DSM-5 diagnosis. Child Psychiatry Hum. Dev. 47 (2), 335–346. http://dx.doi.org/10.1007/s10578-015-0566-7. [PMID: 26202432].
Keen, C.L., Uriu-Adams, J.Y., Skalny, A., Grabeklis, A., Grabeklis, S., Green, K., Yevtushok, L., Wertelecki, W.W., Chambers, C.D., 2010. The plausibility of maternal nutritional status being a contributing factor to the risk for fetal alcohol spectrum disorders: the potential influence of zinc status as an example. Biofactors 36, 125–135.
Kooij, J.J.S., 2013. Adult ADHD: Diagnostic Assessment and Treatment. Springer-Velag, London.
Mattson, S. N., Goh, P., Sadler, M. & Riley, E. P. 2015. Validation of nd-pae diagnostic criteria and suggestions for improvement. American Psychiatric Association 168th Annual Meeting. Toronto, Canada.
Mattson, S.N., Roesch, S.C., Glass, L., Deweese, B.N., Coles, C.D., Kable, J.A., May, P.A., Kalberg, W.O., Sowell, E.R., Adnams, C.M., Jones, K.L., Riley, E.P., CIFASD, 2013. Further development of a neurobehavioral profile of fetal alcohol spectrum disorders. Alcohol.-Clin. Exp. Res. 37, 517–528.
May, P.A., 2015. Faser-USA: methods and initial results. Alcohol. Clin. Exp. Res. 39, 260A.
May, P.A., Baete, A., Russo, J., Elliott, A.J., Blankenship, J., Kalberg, W.O., Buckley, D., Brooks, M., Hasken, J., ABDUL-Rahman, O., Adam, M.P., Robinson, L.K., Manning, M., Hoyme, H.E., 2014. Prevalence and characteristics of fetal alcohol spectrum disorders. Pediatrics 134, 855–866.
May, P.A., Gossage, J.P., 2011. Maternal risk factors for fetal alcohol spectrum disorders: not as simple as it might seem. Alcohol Res. Health 34, 15–26.
Mead, E.A., Sarkar, D.K., 2014. Fetal alcohol spectrum disorders and their transmission through genetic and epigenetic mechanisms. Front. Genet. 5, 154.
Millan, M.J., 2013. An epigenetic framework for neurodevelopmental disorders: from pathogenesis to potential therapy. Neuropharmacology 68, 2–82.
Mukherjee, R.A.S., 2014. FASD in the UK, how far have Services come and where do we Still have to get to Fetal Alcohol Forum, vol. 12, pp. 24–25.
Mukherjee, R.A.S., Hollins, S., Turk, J., 2006. Fetal alcohol spectrum disorder: an overview. J. R. Soc. Med. 99, 298–302.
Mukherjee, R.A.S., Layton, M., Yacoub, E., Turk, J.T., 2011. Autism and autistic traits in people exposed to heavy prenatal alcohol:data from a clinical series of 21 individuals and a nested case control study. Adv. Ment. Health Intellect. Disabil. 5, 43–49.
Mukherjee, R.A.S., Wray, E., Curfs, L., Hollins, S., 2015. Knowledge and opinions of professional groups concerning FASD in the UK. Adopt. Foster. 39, 212–224.
Reynolds, J.N., Valenzuela, C.F., Medina, A.E., Wozniak, J.R., 2015. Proceedings of the 2014 annual meeting of the fetal alcohol spectrum disorders study group. Alcohol 49, 453–460.
Riley, E.P., Infante, M.A., Warren, K.R., 2011. Fetal alcohol spectrum disorders: an overview. Neuropsychol. Rev. 21, 73–80.
Sanders, J., 2013. 'A window of opportunity': the proposed inclusion of Fetal Alcohol Spectrum Disorder in the DSM-5. J. Dev. Disabil. 19, 7–14.
Senturias, Y.S., 2014. Fetal alcohol spectrum disorders: an overview for pediatric and adolescent care providers. Curr. Probl. Pediatr. Adolesc. Health Care 44, 74–81.
Stratton, K., Howe, C., Battaglia, F., 1996. Fetal Alcohol Syndrome: Diagnosis, Epidemiology, Prevention and Treatment. National Academy Press, Washington, D. C.
Streissguth, A.P., Barr, H.M., Kogan, J., Bookstein, F.L., 1997. Primary and secondary disabilities in fetal alcohol syndrome. In: Streissguth (Ed.), The Challenge of Fetal Alcohol Syndrome: Overcoming Secondary Disabilities. Seattle University of Washington Press, Seattle, WA.
Sulik, K.K., 2014. Fetal alcohol spectrum disorder: pathogenesis and mechanisms. Handb. Clin. Neurol. 125, 463–475.
Tan, C.H., Denny, C.H., Cheal, N.E., Sniezek, J.E., Kanny, D., 2015. Alcohol use and binge drinking among women of childbearing age - United States, 2011-2013. MMWR Morb. Mortal. Wkly. Rep. 64, 1042–1046.
World Health Organization, 2011. International Statistical Classification of Diseases and Related Health Problems, 10th revision, edition 2010. World Health Organization, Geneva, Switzerland.