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Diagnostic Outcomes of 27 Children Referred by Pediatricians to a Genetics Clinic in The Netherlands With Suspicion of Fetal Alcohol Spectrum Disorders

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The characteristics of fetal acohol spectrum disorders (FASD) constitute a specific facial phenotype, growth failure and neurodevelopmental defects. Reported FASD prevalences vary widely from 0.08 per 1,000 up to 68.0–89.2 per 1,000. We aimed to evaluate to which extent children referred with a suspicion of FASD, indeed have FASD. We included all 27 children referred to our genetic department with a suspicion of FASD between 2005 and 2010. Nineteen children (70.3%) were of non-Dutch ancestry, and 24 (88.9%) had been adopted. We used both the 4-Digit Code and the Revised Institute of Medicine criteria. More than half of the children did not meet either criteria for the diagnosis of FASD. Of note, after evaluation 8/27 children appeared not to have confirmed prenatal alcohol exposure. Two children referred for suspicion of FASD (neither of which were exposed to alcohol or met the criteria for FASD) had a pathogenic microstructural chromosomal rearrangement (del16p11.2 of 542 KB and dup1q44 of 915 KB). In 22/24 children (91.7%) there were other factors that may have affected their intellectual abilities, such as familial intellectual disability and social deprivation. We recommend a critical approach towards the diagnosis FASD, and to investigate all patients suspected to have FASD for other causative factors including genetic abnormalities.

Key words: fetal alcohol spectrum disorders; fetal alcohol syndrome; DNA micro array

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INTRODUCTION

Fetal alcohol syndrome (FAS) results from maternal alcohol (ab)use during pregnancy and is characterized by a combination of a specific facial phenotype (short palpebral fissures, a thin upper vermillion, and a poorly pronounced philtrum), growth failure and a range of neurostructural, and/or neurodevelopmental defects [Astley, 2011]. FAS is a diagnosis categorized under the umbrella of fetal alcohol spectrum disorders (FASD), which include other probably alcohol related diagnostic categories as well: partial FAS (PFAS), alcohol related neurodevelopmental disorder (ARND), and others [Astley, 2004; Hoyme et al., 2005].

The importance of establishing the diagnosis in individuals with FASD has been stressed repeatedly in literature. Concern has been expressed about the possibility of overdiagnosing or misdiagnosing FASD [Astley, 2004, 2011], especially when facial criteria are relaxed and/or the term ARND is used [Chudley et al., 2005; Hoyme et al., 2005].Information about the possibility of overdiagnosing FASD is lacking however. Diagnostic criteria focus on the sensitivity, in order not to miss FASD [Astley, 2004; Hoyme et al., 2005]. To date, there are no biological markers to confirm or reject the diagnosis with certainty. Therefore several scoring systems have been proposed, of which the 4-Digit Code [Astley, 2004] and the Revised Institute of Medicine criteria [Hoyme et al., 2005] are the most widely used. Since the first description of FAS in the French

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medical literature by Lemoine et al. [1968] and the subsequent description in the seminal paper by Jones et al. [1973], numerous studies have been carried out to determine the prevalence of FASD, reporting figures from 0.08 per 1,000 in Europe and countries elsewhere [Abel, 1995] to up to 68.0–89.2 per 1,000 in the wine producing regions of South Africa [May et al., 2007].

Part of the problem of comparing prevalence studies of FASD is that the term FASD is not specific for disorders caused by maternal alcohol usage and that there is a great variability in case definition by studies using different diagnostic systems. Despite the widely different prevalences reported in the literature, FASD is unanimously regarded as one of the leading causes of intellectual disability [Abel and Sokol, 1986].

From 2005 onwards we have evaluated every child referred to our genetic department with a suspicion of FASD according to a dedicated diagnostic protocol. Here we present the analysis of data collected from all children referred between 2005 and 2010, in order to evaluate the reliability of the suspicion of the diagnosis FASD by pediatricians and geneticists in the Netherlands referring to our centre.

MATERIALS AND METHODS

Patients

All patients referred between 2005 and 2010 to the Pediatric Genetics department at the Academic Medical Center in Amsterdam with a suspected diagnosis of FASD are included in this study. All children were referred by pediatricians or clinical geneticists from other genetic departments in the country.

Institute

The AMC University hospital is an academic medical center in Amsterdam and the largest hospital in the Netherlands. The region of the hospital incorporates 2.8 million inhabitants and 30,000 births per year, covering about one-sixth of the country. Each year approximately 700 children are referred for diagnostic evaluation to the Department of Pediatric Genetics.

Analysis

All children underwent the same set of investigations: documentation about early history including prenatal intoxications with alcohol and other substances, family history, cognitive and motor development, and physical examination. If intellectual disability was present, we carried out a metabolic screening in urine (creatine, guanidinoacetic acid, organic acids, purines, pyrimidines, oligosaccharides, and mucopolysaccharides) and blood (acylcarnitines, amino acids, sterols, transferrin electrofocusing), molecular analysis for fragile X syndrome, chromosome analysis and (in most cases) an array CGH (Agilent 180K oligo-array browser NCBI-build 36.1). Additional studies were performed if dictated by the history and clinical exam.

Two examiners (N.A. and J.M.C.) independently scored clinical data and photographs of the children for the presence of manifestations of FASD, using the 4-Digit Code [Astley, 2004] as well as the Revised Institute of Medicine criteria [Hoyme et al., 2005]. In case of disagreement between the scores of the examiners data and pictures were discussed until agreement was achieved.

Cases were defined as having FASD when they were classified into one of the Revised Institute of Medicine diagnostic categories of FAS, Partial FAS, or ARND [Hoyme et al., 2005], or when they had a 4-Digit Code of A–C or E–H [Astley, 2004].

RESULTS

Demographic Data

From 2005 until 2010, 27 children were referred with a suspicion of FASD; no children in this data set have been referred with the suspicion of a diagnosis other than FASD. During this period, no diagnosis of FASD was made in a child referred to our department for other reasons. Twelve were male (44.4%), mean age at presentation was 6.1 years, 8 children (29.6%) were of Dutch ancestry, and 19 had a non-Dutch ethnic background including 10 Polish children (37.0%; Table I). Twenty-four individuals (88.8%) are living with foster parents.

Additional Studies

The standard work-up showed genetic abnormalities in 2 children which are probably causative: a proximal del16p11.2 of 542 KB and a dup1q44 of 915 KB. It remained unclear whether these abnormalities were de novo, since no DNA was available of the biological parents. The proximal 16p11.2 deletion is a well known pathogenic copy number variant [Bijlsma et al., 2009; Barge-Schaapveld et al., 2011]. The 1q44 duplication is likely pathogenic, due to its size of almost 1 Mb, the presence of several genes in the duplicated region, and the phenotype with intellectual disability in patients with deletions of the same region [Caliebe et al., 2010]. Larger duplications including the 1q44-region are associated with intellectual disability and various congenital abnormalities [Balasubramanian et al., 2009].

FASD Codes

Using the 4-Digit Code [Astley, 2004], we rejected a diagnosis of FASD in 16 children (59.2%), 1 case was classified in category A (3.7%), 2 cases were classified into diagnostic category C (Partial FAS) (7.4%), and 8 cases into diagnostic categories E–H (categorized by us as FASD; 29.6%; Table II). Using the Revised Institute of Medicine criteria, we rejected a diagnosis of FASD in 16 children (59.2%), 3 children were diagnosed with FAS (11.1%), 2 with partial FAS (7.4%), and 6 with an ARND (22.2%). In addition, 2 cases (case 1 and 26) scored positive for a FASD using one classification system and negative using the other (Table II).

Three of the cases are illustrative of the wide variability in symptoms that had led to the suspicion of FASD. Case 14 is a 7-year-old female foster child from Poland and was diagnosed with FASD, since she scored as Partial FAS with confirmed maternal alcohol exposure using the 4-Digit Code and scored as FAS with confirmed maternal alcohol exposure using the Revised Institute of

TABLE I. Demographic Data of the Included Children

Case number	Age at presentation	Sex	Adopted	Ethnicity	Other risk factors
1	4	f	Yes	Colombia	—
2	3	m	Yes	Slovakia	A C
3	12	m	Yes	Brazil	C
4	6	f	No	Afro-American	A, B, and C
5	8	m	Yes	The Netherlands	A
6	10	m	Yes	The Netherlands	B
7	6	f	Yes	Poland	A and B
8	10	m	Yes	Marocco/Suriname/China	D
9	3	f	Yes	Marocco/Unknown	D
10	1	m	Yes	The Netherlands/Italy	B and C
11	5	f	Yes	Poland	C
12	8	f	Yes	Poland	C
13	9	f	Yes	The Netherlands	C
14	7	f	Yes	Poland	C
15	4	f	Yes	Poland	—
16	4	f	Yes	Poland	A
17	8	m	Yes	Poland	A
18	4	v	No	The Netherlands	B
19	7	m	Yes	Colombia	C
20	5	f	Yes	Poland	C
21	8	f	Yes	Poland	C
22	4	m	Yes	Poland	D
23	3	m	Yes	The Netherlands	B
24	4	f	Yes	The Netherlands	B and C
25	15	m	No	The Netherlands	A, B, and C
26	3	m	Yes	Marocco/The Netherlands	B and C
27	3	f	Yes	The Netherlands	C

Age: in years; sex: m, male; f, female; other risk factors: —, no other etiological risk factors for mental retardation; A, At least one first- and/or two second-degree relatives with intellectual disability; B, Substance use other than alcohol during pregnancy; C, Affective deprivation during the first year of life; D, No information available about confounding factors.

Medicine Criteria (Fig. 1). Case 17 is a 8-year-old male foster child from Poland who scored No FASD by both FASD diagnostic systems, in whom array CGH showed a duplication of chromosome 1q44 (Fig. 2). Case 7 is a 6-year-old female foster child from Poland scored in category V of the 4-Digit Code (no sentinel physical findings or CNS abnormalities detected; no alcohol exposure) and having no FASD according to the Revised Institute of Medicine-criteria (Fig. 3) in whom array CGH showed a proximal deletion of 16p11.2 of 542 KB. Although both FASD systems correctly ruled out a diagnosis of FASD in cases 7 and 17 who appeared to have a chromosomal abnormality, it is interesting to note that both these cases were referred with a suspected diagnosis of FASD.

Other Risk Factors

Data on risk factors that could have affected the intellectual abilities of our subjects were available in 24/27 cases (88.9%). In total, 22 of these 24 cases have been exposed to one or more etiologic factors other than alcohol that may have affected their intellectual abilities (91.7%): 7 children (29.2%) have at least one first-degree or two second-degree family members with an intellectual disability; 9 children (37.5%) have been exposed to possibly teratogenic substances in utero other than alcohol (nicotine, cannabis, cocaine, antiepileptic drugs, paroxetine, alprazolam, oxazepam, and temazepam); and 15 (62.5%) suffered from affective deprivation during their early childhood (Table I). Of the 11 cases finally diagnosed with FASD using the 4-Digit Code, all had at least one risk factor as (additional) cause for their intellectual disability and two (18.1%) had a first-degree relative with intellectual disability. Of the 11 cases diagnosed with FASD using the Revised Institute of Medicine criteria, 10/11 (90.9%) had at least one other risk factor (Tables I and II).

DISCUSSION

In the present study group the presumed diagnosis of FASD could not be confirmed in more than half of the referred cases. Two of 27 children turned out to have a genomic imbalance that may explain their phenotype well. Several other papers reported "FASD patients" who were proven to have a demonstrable genetic defect in second instance [Römke et al., 1987; Müller et al., 1993; Stoler, 1999]. Obviously genetic or other causes of intellectual disabilities can co-occur with alcohol abuse during pregnancy by coincidence [Bingol et al., 1987]. Indeed, it has been recommended that a classification of a case as FASD "in no way should imply that the diagnostician need not consider alternate or co-existing syndromic, medical or psychiatric conditions" [Astley, 2004]. Although in our

TABLE II. 4-Digit Diagnostic Codes and Revised Institute of Medicine Criteria for FASD in Our 27 Included Cases, With the Results of Genetic Diagnostics

Case number	Growth deficiency[a]	FAS facial features[b]	CNS damage[c]	Gestational alcohol exposure[d]	4-Digit Code	4-Digit Code diagnostic category	4-Digit Code diagnostic category name	Revised Institute of Medicine criteria	Test results array CGH if remarkable
1	2	2	3	2	2232	L	No FASD	IV—partial FAS	
2	2	4	4	3	2443	A	FAS	I—FAS	
3	1	1	2	2	1122	N	No FASD	No FASD	
4	1	1	4	2	1142	L	No FASD	No FASD	
5	1	2	2	2	1222	N	No FASD	No FASD	
6	2	2	3	4	2234	F	SE/AE (FASD?)	VI—ARND	
7	1	2	1	1	1211	V	No FASD	No FASD	Del 16p11.2
8	1	1	1	2	1112	P	No FASD	No FASD	
9	1	2	4	4	1244	F	SE/AE (FASD?)	VI—ARND	
10	1	1	1	4	1114	J	No FASD	No FASD	
11	4	1	1	4	4114	I	No FASD	No FASD	
12	1	1	1	4	1114	J	No FASD	No FASD	
13	1	1	1	3	1113	J	No FASD	No FASD	
14	2	3	4	4	2344	C	Partial FAS	I—FAS	
15	1	2	1	4	1214	J	No FASD	No FASD	
16	2	1	4	2	2142	L	No FASD	No FASD	
17	1	1	4	2	1142	L	No FASD	No FASD	Dup1q44
18	1	1	3	4	1134	F	SE/AE (FASD?)	VI—ARND	
19	4	1	4	4	4144	E	SF–SE/AE (FASD?)	VI—ARND	
20	4	3	4	4	4344	C	Partial FAS	I—FAS	
21	1	1	1	4	1114	J	No FASD	No FASD	
22	3	2	3	4	3234	E	SF–SE/AE (FASD?)	VI—ARND	
23	1	1	1	4	1114	J	No FASD	No FASD	
24	4	2	1	4	4214	I	No FASD	No FASD	
25	2	1	4	4	2144	F	SE/AE (FASD?)	VI—ARND	
26	4	2	2	3	4223	G	ND/AE (FASD?)	No FASD	
27	4	3	2	4	4324	G	ND/AE (FASD?)	III—Partial FAS	

SE, static encephalopathy; SF, sentinel findings; AE, alcohol exposed; ND, neurobehavorial disorder; ARND, alcohol related neurodevelopmental disorder.
Growth deficiency, FAS facial features, CNS damage, gestational alcohol exposure [Astley, 2004].
[a]1, none; 2, mild; 3, moderate; 4, severe.
[b]1, none; 2, mild; 3, moderate; 4, severe.
[c]1, unlikely; 2, possible; 3, probable; 4, definite.
[d]1, no risk; 2, unknown; 3, some risk; 4, high risk.

2 cases who appeared to have chromosomal imbalances the diagnosis FASD was correctly ruled out by both FASD diagnostic systems, these two cases nevertheless were referred for suspicion of FASD. Our observation stresses the importance to consider other diagnoses when FASD is suspected and to perform adequate additional investigations.

If a child meets FASD criteria, it is assumed that at least some of the clinical manifestations may be caused by the maternal alcohol use during pregnancy. Other etiologic risk factors, however, are present in a large majority of cases. Simultaneous use of other substances during pregnancies by mothers that use alcohol, is well known [Day et al., 1993; Gladstone et al., 1997; Donnelly et al., 2008] and was found in the present group as well. The high frequency of first-degree and second-degree relatives with intellectual disability points to frequent co-occurrence of maternal alcohol abuse during pregnancy with genetically determined causes of the intellectual disability. It is likely that both parental intellectual disability and maternal alcohol abuse increases the risk of social deprivation, which may have an additional negative influence of the development of the child [Nordberg et al., 1993; Beckett et al., 2007]. Hence, FASD appears to co-occur with numerous other etiologic factors that might explain some or all of the somatic problems and cognitive delay.

The present study was not designed as an epidemiological study, and no reliable statements about the prevalence of FASD in the Netherlands can be made based on our data only. Still, we were surprised with the referral of such a small number of children with a suspicion of FASD in 5 years time. Taking into account that more than half of the children from the present study who were diagnosed with FASD had a non-Dutch ancestry, it may appear that FASD is quite uncommon in the Dutch native population. However, it would need a dedicated epidemiological study to confirm this. Underrecognition of FASD is a common concern in the literature [Van Balkom et al., 1996; May et al., 2006] so it remains possible that FASD is more common in the Netherlands than our data suggest. In a study describing the results of a questionnaire among all Dutch

FIG. 1. Case 14 (see Table I). This girl was born in Poland as the sixth child of two alcohol dependent parents. Delivery was at 38 weeks gestation and her birth weight was 1,900 g (<p10). Her mother has been documented to drink large amounts of alcohol during the pregnancy. When this child was 2.5 years old, she was legally removed from parental care because of child neglect. At the age of 5 years, she was adopted by foster parents from the Netherlands. At physical examination at the age of 7 years, she measured 122.8 cm (2 cm < P50), her weight measured 20.5 kg (<−2 SD weight for length). She had a head circumference of 46.7 cm (0.5 cm < −2.5 SD). Neuropsychological testing showed an IQ of 55 with a harmonic profile, poor attention and concentration, hyperactivity and impulsive behaviour. Additional genetic testing did not show any abnormalities.

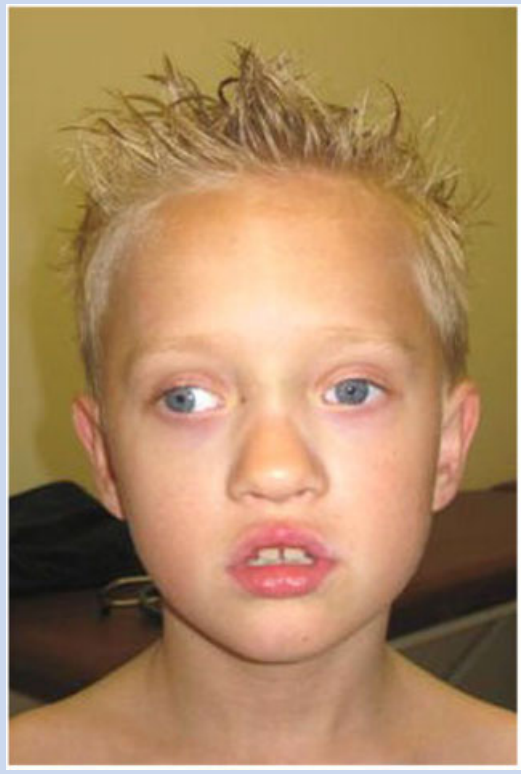

FIG. 2. Case 17 (see Table I). This boy is the son of Polish parents. He lived in Poland until he was adopted by Dutch foster parents at the age of 5 years. This boy was suspected of FASD although it has never been confirmed that his mother used alcohol while pregnant, nor has she ever been described as being alcohol dependent. From official documents, it is known that the mother of this child is intellectually impaired. On physical examination his length was 128.6 cm (−1.0 SD), his head circumference was 52.4 cm (0 SD) and his weight was 28.0 kg (0.0 SD). His face shows several dysmorphisms: an upward slant of both eyes without short palpebral fissures, a short but normally profiled philtrum and a normal thickness of the vermillion border of the upper lip. He has a narrow nasal bridge at the nasal root while the lower part and tip of the nose are wide. There is a myopia of −11 diopter bilaterally. Neuropsychological testing of this boy showed an IQ of 53. An array CGH revealed a duplication of chromosome 1q44 of 915 KB.

pediatricians, who reported 39 cases of suspected FASD in a 2-year period (2007–2008), it has been suggested the prevalence of FASD in the Netherlands is low [Van Wieringen et al., 2010]. The latter authors estimated that the prevalence of FASD in the Netherlands might be approximately 1 in every 10,000 births. On the other hand, as FASD is well-known in the Netherlands and has been an important topic in the education of pediatricians, it seems less likely that this low prevalence is the result of major underrecognition. We conclude that the only sensible statement to be made on the prevalence of FASD in the Netherlands is that a more formal epidemiologic study is needed for this.

In the literature there is a clear aim towards trying to avoid underdiagnosis of FASD and some diagnostic criteria are designed as such. The present, admittedly small study may indicate that FASD can be prone to overdiagnosis as well, as about half of the cases referred by pediatricians with a diagnosis or suspicion of FASD appeared not have FASD. Since an incorrect diagnosis of FASD can be harmful and stigmatizing to the child and the parents, overdiagnosis should be avoided as well.

In conclusion we recommend a critical approach towards the diagnosis FASD in a clinical setting. In concert with earlier recommendations [Astley, 2004; Hoyme et al., 2005] we emphasize that a suspicion of FASD in a child should not prevent a physician from performing a thorough further evaluation to probe the presence of other causes of the manifestations in the child. Further improvement of education of pediatricians and other physicians with respect to FASD is warranted, to reduce the number of children falsely put under suspicion of FASD, and so reducing the socio-

FIG. 3. Case 7 (see Table I). This girl was born in Poland and adopted at the age of 1.5 years by Dutch foster parents. A Dutch employee of the foster parents organization stated that the biological mother had used alcohol during her pregnancy and suggested that the girl has FASD. We requested medical information from Poland and from written documents it appeared that, according to the Polish doctor, the mother had used anti-epileptic medication during pregnancy and no alcohol. At the age of 9 years, this girl had an IQ of 84 with language impairment, and went to a school for children with special educational needs. Array CGH showed a deletion of 16p11.2 of 542 KB.

emotional burden of this diagnosis on children and their (foster) parents.

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