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Validation of the Polish Version of the Washington 4-Digit Diagnostic Code for the Assessment of Fetal Alcohol Spectrum Disorders

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Summary

Aim. The aim of this paper is a quantitative assessment of FASD facial phenotype in the Polish population using the Polish version of the 4-Digit Diagnostic Code.

Methods. The study covered 2 groups of children: 30 children aged 4–7 and 30 children aged 8–11 with a facial phenotype characteristic for the Fetal Alcohol Syndrome (FAS). The control group consisted of 60 children (4–11 years old) developing normally. We compared 3 facial features (small palpebral fissure lengths, smooth philtrum and thin upper lip). The repeatability, conformity and diagnostic accuracy of particular dysmorphic features of the study were assessed.

Results. Obtained values for palpebral fissure were "poor", "good" and "very good", for philtrum "good" and "very good" and for upper lip "good" and "very good". As for conformity, values for palpebral fissure were "moderate" and 'good", for philtrum – "good" and for upper lip also "good". In the experimental group, the FAS diagnostic criteria were met by 13 subjects, partial FAS criteria were met by 37 subjects and the criteria of static encephalopathy with no FAS phenotype were met by 2 subjects. None of the subjects in the control group met these criteria.

Conclusions. The pictorial scale for the assessment of the facial dysmorphic features proved to be a useful tool in the clinical diagnostics of FAS in the Polish conditions. Due to the problems associated with the measurement of the palpebral fissure, it is necessary to verify the normal growth charts for the Polish population.

Key words: 4-Digit Diagnostic Code, fetal alcohol syndrome, facial dysmorphic features

Introduction

The term Fetal Alcohol Spectrum Disorders (FASD) defines a continuum of disorders differing in terms of intensity of physical changes (specific facial dysmorphic features and specific features of growth) and functional changes (cognitive processes, behavioral and emotional disorders) caused by maternal consumption of alcohol during pregnancy [1]. However, it is not used as a clinical diagnosis; therefore a patient cannot be diagnosed with FASD. The umbrella term FASD includes the following:

1. Fetal Alcohol Syndrome (FAS), which constitutes only around 10% of FASD diagnoses;
2. Partial Fetal Alcohol Syndrome (pFAS);
3. Alcohol Related Neurodevelopmental Disorders (ARND);
4. Alcohol Related Birth Defects (ARBD);
5. Prenatal Alcohol Exposure (PAE).

The 4-Digit Diagnostic Code was created in 1997. It was created as a tool to address the limitations associated with the conventional – based on the subjective assessment of a testing person – approach to diagnosing persons with prenatal exposure to alcohol [2]. To develop this method vast medical documentation was used which covered more than 2,000 patients (from a new born to a 53 year-old patient) who were diagnosed within the FAS Diagnostic and Prevention Network [3]. Diagnosing with the 4-Digit Diagnostic Code consists in the assessment of the intensification of four key diagnostic characteristics of FASD in the following order:

(1) growth deficiency (understood as deficiency in body mass and length);
(2) facial phenotype characteristic for FAS;
(3) CNS abnormalities;
(4) prenatal alcohol exposure.

Intensification of each of these features is assessed on the 4-point Likert scale, where "1" reflects complete lack of a FAS feature and "4" means a strong presence of a FAS feature. As a result, the 4-Digit Diagnostic Code emerges, where the Code "4444" means the most severe expression of FAS, i.e.:

- significant growth deficiency (rank of "4");
- clear facial dysmorphic features – the presence of 3 FAS dysmorphic features: short palpebral fissures (below – 2 SD), smooth philtrum and thin upper lip (rank of "4"). In the diagnostic language all three features are defined as marker features;
- structural/neurological evidence of CNS damage (rank of "4");
- confirmed prenatal exposure to high levels of alcohol (rank of "4").

Eventually, we obtain 102 codes describing FASD in the following subcategories:

- Fetal Alcohol Syndrome (FAS);

- Partial Fetal Alcohol Syndrome (PFAS);
- Static Encephalopathy/Alcohol-Exposed (SE/AE);
- Neurobehavioral Disorder/Alcohol-Exposed (ND/AE) [2].

The studies conducted in the last two decades confirmed the sensitivity and specificity of palpebral fissure length, the degree of philtrum smoothness and the degree of upper lip thinness for FAS. Moreover, attempts have been made to define the magnitude of expression of these features required to maximize the sensitivity and specificity. The clinical validity of using these features has been confirmed in the population screening, epidemiological and experimental tests which proved that there are correlations between the presence of the above-mentioned facial abnormalities and brain damage/dysfunction [4, 5].

To measure the palpebral fissure length (PFL) the normal PFL charts are used. However, the available normal PFL charts for Caucasians vary significantly [6–8]. Authors question their accuracy and sensitivity. In 2010, new PFL charts for children aged 6–16 (girls and boys) were published [8]. The Scandinavian PFL charts 0–18 are also correct, adjusted to the changes in palpebral fissure length across lifespan [9]. Since patients at different age are diagnosed (from newborns to adults with FASD), the University of Washington recommends the Scandinavian charts which take into consideration changes that occur in the course of life. The charts are presented below (the relation between age and PLF) (by courtesy of Astley; 2013)

1. Thomas chart. Curves poorly matched. The curve does not agree with the actual growth trajectory from birth to 16 years of age. Growth speed seems to be too fast from birth to 3 years of age and too slow below 3 years;
2. Hall's chart. Accurate growth trajectory, but PFL is too long;
3. Canadian chart. Accurate growth trajectory, correct PFL, but the chart starts from 6 years of age;
4. Norwegian chart by Strömland. Accurate growth trajectory, correct PFL, the chart covers the whole age group;
5. PFL for 822 children with FAS and FASD diagnosed in the FASD Clinic of the University of Washington in Seattle.

Figure 1 shows the curves of charts presenting the relation between age and PLF for various measurement charts.

Aim

The aim of this paper is a quantitative assessment of facial dysmorphic features using the Polish version of the 4-Digit Diagnostic Code.

The project was approved by the Bioethical Committee of the Medical University of Silesia, No. KNW/0022/KB1/51/1/10.

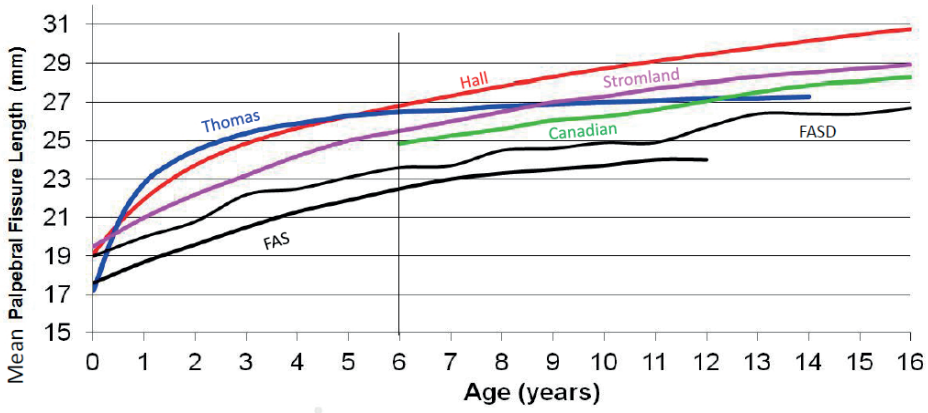

Figure 1. **Curves of charts presenting the relation between age and PLF on various measurement charts**

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Epidemiology/Pediatrics, FAS DPN University of Washington.

Material and Methods

Subjects of the study

Two groups of children were chosen from the database of around 300 children reported to the Laboratory of Developmental Disorders Diagnostics and Therapy in Ledziny, Poland and consulted in the Department of Psychiatry and Psychotherapy of Developmental Age of the Chair of Psychiatry and Psychotherapy of the Medical University of Silesia located in the Jan Paul II Pediatric Center in Sosnowiec, Poland. The first group consisted of 30 children aged 4–7 and the second group – 30 children aged 8–11 with the FAS facial dysmorphic features. The selection to the study group was made by an expert on the basis of diagnostic criteria described in ICD-10 for the fetal alcohol syndrome (Q 86.0 – Fetal Alcohol Syndrome (Dysmorphic)) and further defined by the institute of Medicine in 1996. The above-mentioned expert was a professional specializing in psychiatry of children and adolescents with a long-time clinical experience both in differential diagnostics of syndromes with facial dysmorphic features and in cognitive, emotional and behavioral disorders of children with a positive pregnancy-labor history (including the exposure to alcohol). The study was supplemented with the information derived from medical history. The control group consisted of 60 children (4–11 year-olds), the patients of the John Paul II Pediatric Center in Sosnowiec – with no facial dysmorphic features, developing normally, which was defined on the basis of the medical history and physical examination. The study compared the assessment results of expression of 3 facial dysmorphic features (shortened palpebral fissures, smoother philtrum and thinness of upper lip) which are typical for FAS [10].

The manner of assessment with the 4-Digit Diagnostic Code

Three digital photos of the face of each child participating in the study were taken, applying the recommendation of the University of Washington (FAS Diagnostic and Prevention Network). The photos were coded by the expert (double blind trial), which enabled the testing persons to identify patients and their affinity to the control or study group.

Two diagnosticians, who did not have any contact with each other, were supposed to perform the following tasks:

I. To measure the palpebral fissure length (PFL) — (in case of FAS the marker result is – 2 or more standard deviations (SD) below the norm. The PFL measurement was performed after the photo was taken, on the computer screen. During the measurement the diameter of the paper sticker (A) and the distance between the exocanthion and endocathion (B) and the PFL was calculated (C) using the actual diameter of the sticker D = 1.9 mm: C = A x D: B, taking into account the calibration factor. At present, the software available at the University of Washington is believed to be the most accurate, confirmed by various studies, measurement procedure [11].

   Figure 2 presents the proper position of eyeballs while the photo is taken.

II. To assess the degree of philtrum smoothness (in case of FAS – the rank of 4 or 5 in the pictorial scale – Lip Philtrum Guide, LPG)

III. To assess the degree of upper lip thinness (in case of FAS – the rank of 4 or 5 in the pictorial scale – Lip Philtrum Guide, LPG).

The pictorial scale to assess the FAS dysmorphic features (The Lip-Philtrum Guide, LPG) is a 5-point pictorial scale used by the FAS Diagnostic & Prevention Network at the University of Washington in Seattle to measure precisely the smoothness of

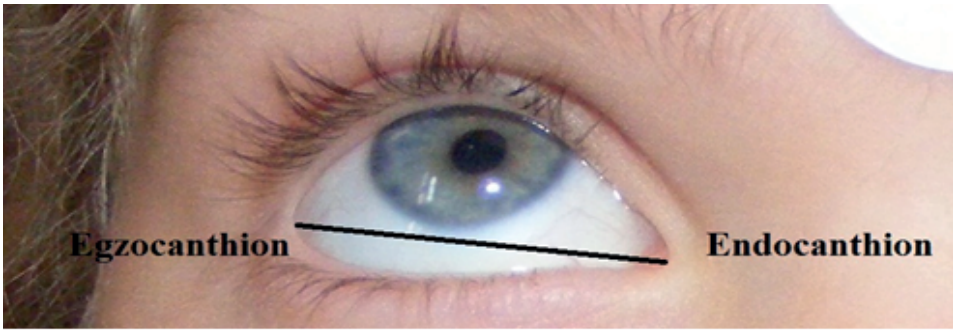

Figure 2. **Proper position of eyeballs while the photo is taken**

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philtrum and the degree of thinness of the upper lip. The photos assessed between rank 1 and 5 show a typical expression of dysmorphic features characteristic for the alcohol-related congenital developmental disorders: smoothness of philtrum and thin upper lip. Photo No. 1 in the pictorial scale shows an example of a patient with a very deep philtrum and full upper lip. Subsequent photos (assessed in the 5-point Likert scale) present more and more smooth philtra and less and less prominent and thinner upper lips. The size of the original scale is 20 x 5 cm.

Figure 3 presents the LPG pictorial scale for the assessment of the facial dysmorphic features.

The validation procedure of the FAS pictorial scale covered the assessment of repeatability, conformity and diagnostic accuracy of the study results for particular dysmorphic features, in the scope of philtrum, upper lip and palpebral fissure [10]. The morphological assessment of face (on the basis of the photos) was performed independently by two diagnosticians (Diagnostician A and Diagnostician B). Each Diagnostician examined all and the same children and each child was examined twice. This procedure enabled to assess the repeatability of the results of double measurement in the same child by each Diagnostician (the assessment of variability "inside an observer") as well as the assessment of compatibility of measurement results performed by two Diagnosticians in the same child (the assessment of variability "between observers").

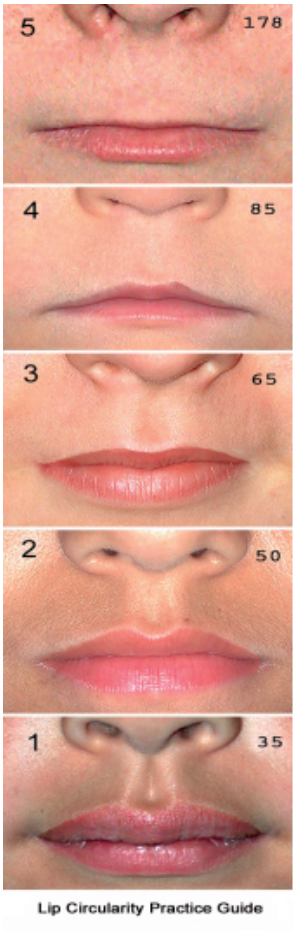

Figure 3. **LPG pictorial scale for the assessment of the facial dysmorphic features**

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Methods of statistical calculations

The analyses of repeatability and measurement accuracy of philtrum and upper lip – in the consecutive and independent analyses – used four types of variables presentation:

1. The result on the original scale (1–5 points on the FAS pictorial scale);
2. The result on the three-level clinical scale:
   a) dysmorphic features "-", when the result on the point scale corresponds to the photo No. 1 or 2 on the pictorial scale, since both photo No. 1 and 2 on the pictorial scale mean the lack of FAS facial dysmorphic features;

b) dysmorphic features "+/-", when the result on the point scale corresponds to the photo No. 3 on the pictorial scale, since photo No. 3 on the pictorial scale means the presence of the so-called mild dysmorphic features which is characteristic for 50% of population and is of no diagnostic significance;
c) dysmorphic features "+", when the result on the point scale corresponds to the photo No. 4 or 5 on the pictorial scale, since both photo No. 4 and 5 on the pictorial scale mean the presence of facial dysmorphic features which is characteristic for FAS – this variable is clinically significant;

3. The result on the two-level clinical scale:
   a) dysmorphic features "no", when the result on the point scale corresponds to photo No. 1 or 2 on the pictorial scale;
   b) dysmorphic features "yes", when the result on the point scale corresponds to photo No. 3, 4 or 5 on the pictorial scale – a variable of clinical significance;
4. The result on the two-level clinical scale:
   a) dysmorphic features "no", when the result on the point scale corresponds to photo No. 1, 2 or 3 on the pictorial scale;
   b) dysmorphic features "yes", when the result on the point scale corresponds to photo No. 4 or 5 on the pictorial scale – a variable of clinical significance.

For the assessment of the palpebral fissure, the analysis of repeatability and length measurement accuracy was conducted against the results of the original measurements (in mm), and then after transforming the original quantitative variable into the variable of clinical significance. To do so, the Hall's chart was used, because it was recommended to assess PFL at the time this study was performed [6].

For the statistical analysis the following manners of variable presentation were used:

– the result of PFL on the original scale (mm);
– the result on the three-point scale defined by the "standard deviations criterion": a fissure is correct when the value does not exceed – 1 SD; a fissure is doubtful when the value lies between – 1 and – 2 SDs; a fissure is incorrect when the value exceeds – 2 SDs;
– the result on the two-point defined by the "standard deviations criterion": a fissure is correct when the value does not exceed – 2 SD: a fissure is incorrect when the value exceeds – 2 SDs;

For the qualitative variables (the reading regarding philtrum, upper lip and the qualitative presentation of PLF) the percentage of identical readings made by Diagnostician A and B and the result of kappa test were the basic statistical measurements of accuracy and repeatability. Due to the multi-level construction of the variable, the so-called weighted kappa statistic (theoretical distribution: 0–1) and its 95% confidence interval was applied. Following the criteria recommended in literature, the following classification levels of kappa statistic were assumed:

value 0.00–0.40: poor repeatability/accuracy;
value 0.41–0.60: moderate repeatability/accuracy;
value 0.61–0.80: good repeatability/accuracy;
value 0.81–1.00: very good repeatability/accuracy;

For the quantitative variable (the original scale of reading of the PLF) an additional analysis was applied of linear correlation as well as Bland and Altman plot which consisted in determination of difference regression against the mean value of the results [12]. The analysis allowed for all the elements of the strategy proposed by Bland and Altman, especially the following: the mean value of differences and standard deviation were calculated, the 95% confidence interval of differences was determined (95% CI).

The accuracy analysis used the dichotomous result of dysmorphic features assessment, contrasting the result of dysmorphic features "-" (negative test: dysmorphic features = no) with the result including changes of the type: dysmorphic features "+/-" or dysmorphic features "+" (positive test: dysmorphic features = yes).

The accuracy of results of both assessments performed independently by both Diagnosticians A and B was also analyzed. To interpret the diagnostic accuracy the classification of diagnostic odds ratio was used (DOR) [10].

Results

The analysis covered data from the examination of 120 children, where 60 children were healthy and 60 children presented FAS features.

Each dysmorphic feature in each child was assessed four times (2 examinations performed by two Diagnosticians).

Distribution of dysmorphic features in the experiment and control groups was as follows:

1. For philtrum, in the clinical group anomalies were found in 56 children (Diagnostician A, examination 1), 57 children (Diagnostician A, examination 2), 55 children (Diagnostician B, examination 1), 56 children (Diagnostician B, examination 2). In the control group anomalies were found in 0 children (Diagnostician A, examination 1), 3 children (Diagnostician A, examination 2), 4 children (Diagnostician B, examination 1), 8 children (Diagnostician B, examination 2).
2. For the upper lip, in the clinical group anomalies were found in 51 children (Diagnostician A, examination 1), 48 children (Diagnostician A, examination 2), 45 children (Diagnostician B, examination 1 and 2). In the control group anomalies were found in 3 children (Diagnostician A, examination 1), 6 children (Diagnostician A, examination 2), 2 children (Diagnostician B, examination 1), 6 children (Diagnostician B, examination 2).

3. For palpebral fissures, in the clinical group anomalies were found in 59 children (Diagnostician A, examination 1), 60 children (Diagnostician A, examination 2), 60 children (Diagnostician B, examination 1 and 2). In the control group anomalies were found in 51 children (Diagnostician A, examination 1), 57 children (Diagnostician A, examination 2), 54 children (Diagnostician B, examination 1), 56 children (Diagnostician B, examination 2).

Such a high result of confirmed dysmorphic features in palpebral fissures seemed to question the existing norms (Hall's charts), which was confirmed in other studies, which in turn led to withdrawal of recommendation of leading diagnostic centers for these charts. At present, the Norwegian Strömland charts are recommended and they are used while diagnosing with the 4-Digit Diagnostic Code.

In the validation procedure (the assessment of repeatability, compatibility and diagnostic accuracy) the following results were obtained.

In the scope of repeatability (the assessment of repeatability of the results of double measurement in the same child by each Diagnostician), in accordance with the classification levels of kappa statistic the following values were obtained:

1. For palpebral fissure the repeatability at poor, good and very good levels.
2. For philtrum the repeatability at good and very good levels.
3. For upper lip the repeatability at good and very good levels.

In the scope of conformity, the assessment consisted in the measurement of facial dysmorphic features conducted by two Diagnosticians as well as the assessment of differences between Diagnostician A and Diagnostician B in the two subsequent tests. Within this scope, the following values were obtained, which were in line with the classification levels of the kappa statistic:

I.1.1. For palpebral fissure the conformity at the moderate level was obtained during the first measurement and at good level during the second measurement. Better values were obtained during the second measurement, which suggests that better management with the tools and the effect of learning have a positive impact on the quality of results.

I.1.2. For philtrum the conformity at good level was obtained. The results of kappa test revealed a better conformity of readings for the second measurement as compared with the first measurement, which may suggest a better proficiency in using the tool in the subsequent measurement.

I.1.3. For upper lip the conformity at good level was obtained. The subsequent results of kappa test revealed a better conformity of readings in the case of the second measurement as compared with the first reading.

Upon transforming the quantitative variable (measurement in mm) into the three-level clinical variable (1. palpebral fissure correct; 2. palpebral fissure doubtful; 3. palpebral fissure incorrect) and the two-level variable (1. palpebral

fissure correct; 2. palpebral fissure incorrect) the conformity analysis presented in the following way:

For the three-level clinical variable:

- poor conformity in the result of the first measurement;
- good conformity in the result of the second measurement.

For the two-level clinical variable:

- poor conformity in the result of the first measurement;
- conformity in the result of the second measurement on the verge of good and very good.

The assessment of diagnostic accuracy was conducted by calculating the ratio of general accuracy, sensitivity, specificity as well as the diagnostic odds ratio. The results of accuracy results analysis of both measurements conducted independently by both Diagnosticians in accordance with the classification of diagnostic odds ratio (DOR) were as follows.

With the two-level clinical variable (negative test: facial dysmorphic features = no) and contrasting this category with the unequivocally pathological result (facial dysmorphic features = yes) the DOR above 10 was obtained, which – according to the suggested classification – means "significant increase of probability, often sufficient to confirm the presence of a disease". In the process of FASD diagnosis, the ranks of 1 and 2 on the 5-point pictorial scale are treated as correct (the lack of facial dysmorphic features) and the ranks of 4 and 5 as incorrect (clear facial dysmorphic features), and using the ranks of 1 or 2 and 4 or 5 in the final diagnosis has no effect on the final diagnosis.

For upper lip, the obtained DOR was low for the criterion of pictorial scale assessment 1–5 (1 and 2 = correct value meaning the lack of facial dysmorphic features, 3 = intermediary value (mild facial dysmorphic features); 4 and 5 = incorrect value (clear facial dysmorphic features). While using the two-level clinical variable the obtained DOR value was above 10, which – according to the suggested classification – means "significant increase of probability, often sufficient to confirm the presence of a disease".

For palpebral fissure, the obtained DOR was below 2, which means "the lack of change in the probability of disease presence". However, it should be stressed that both Diagnosticians recognized a very small number of correct palpebral fissures (in three and four children, respectively), so the feature believed to be the marker in diagnosing FAS was present also in almost all the children of the control group. This may suggest that there is a necessity to verify the normal PFL charts for the Polish population. This verification together with new recommendations took place in 2013 – after the present study had been concluded.

To sum up, FAS was diagnosed in 13 subjects from the experimental group (21.7%), the pFAS criteria were met by 37 subjects (61.7%) and static encephalopathy without

FAS phenotype was present in 2 persons from this group (3.3%). None of the persons in the control group revealed the above three disorders. Neurobehavioral disorders manifested by retardation in speech development, motor dysfunctions, and dysfunctions in home and school functioning were present in 3 subjects in the experimental group and 2 in the control group. Growth retardation and/or FAS facial phenotype with no abnormalities within CNS were present in 2 persons in the experimental and 1 in the control group. In the study group there were no subjects without recorded growth retardation or FAS facial dysmorphic features, as well as structural, neurological and functional abnormalities – only prenatal alcohol exposure was confirmed. It should be noted that the basic criterion for inclusion to the experiment group was the presence of facial dysmorphic features confirmed during the physical examination without using the diagnostic tools.

Discussion

The first worldwide validation of the 4-Digit Diagnostic Code was conducted under the supervision of Astley on the basis of data regarding 1,400 patients (from newborns to adults) in the FAS Diagnostic and Prevention Network, University of Washington in Seattle who were examined between 1993 and 2005 [3]. In the study group, only 4% of subjects were diagnosed with FAS, 7% met the diagnostic criteria of pFAS, 28% revealed static encephalopathy (with no FAS facial phenotype), 52% presented neurobehavioral anomalies and 2% revealed growth retardation and/or FAS facial phenotype, but there were no CNS anomalies observed. However, in 7% of the subjects no growth retardation or FAS facial dysmorphic features were observed, neither were there any structural, neurological and functional abnormalities – the only factor present was the prenatal alcohol exposure [3].

The validation of the tool conducted by Astley reveals that the rank of "4" for facial dysmorphic features linked with prenatal alcohol exposure is characteristic for FAS. The assessment of facial dysmorphic features with the 2D photo and the Likert scale in Astley's study is characterized by 100% sensitivity, 99.8% specificity and 85.9 DOR. This is the summary of the study conducted on the group of 2,500 children examined in the FAS DPN Center over the period of 10 years (1999–2009) [3]. Between 1992 and 2012 there were 35 publications documenting this process.

The results of the study on the co-occurence of dysmorphic features both in philtrum and upper lip – while contrasted with the lack of both changes – are manifested by a very high (100%) sensitivity and specificity in the case of changes assessed in this study by Diagnostician A and a high sensitivity (91.6%) and very high specificity (100%) in the case of Diagnostician B. The results regard only the clinical group. In the case of the study in both categories (clinical and control group together), the sensitivity and specificity decreases, which confirms the usefulness of the tool for diagnosing children with facial dysmorphic features, so it is designed for detecting anomalies [10].

The validation process of the 4-Digit Diagnostic Code presented in this paper is the first in Europe. Polish scientists have been in touch with the University of Washington since 2000, when the head of the Clinic, the retired professor Ann Streissguth shared her scientific outcomes within FASD. Ten years later, in agreement and co-operation with the successor of prof. Streissguth, prof. Susan Astley, under the auspices of the Department of Psychiatry and Psychotherapy of Developmental Age of the Chair of Psychiatry and Psychotherapy of the Medical University of Silesia in Katowice located in the John Paul II Pediatric Center Sp. z o.o. in Sosnowiec, the works on the Polish version of this most frequently used worldwide diagnostic tool commenced. As a result, we are in possession of the FADS Diagnostic Guide in the Polish version [13] as well as the validated pictorial scale to assess facial dysmorphic features. We also commenced the series of training courses for interdisciplinary teams consisting of medical doctors, psychologists and therapists who would like to use this standardized tool in the diagnostic and scientific work.

As a conclusion it should be noted that the pictorial scale to assess facial dysmorphic features proved to be a useful tool in clinical diagnostics and creating diagnostic procedures in the Polish conditions, where it underwent the validation procedure for the first time in Europe. Due to the problems associated with the measurement of palpebral fissure it is necessary to verify the normal PFL charts for the Polish population.

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