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Epidemiological survey of 214 families with bladder exstrophy-epispadias complex (BEEC)

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Abstract

Purpose—To identify causative non-genetic and genetic risk factors to the bladder exstrophy-epispadias complex (BEEC).

Materials and Methods—237 BEEC families were invited to participate and information was obtained from 214 families, mainly comprising European countries.

Results—Two families showed familial occurrence. Male predominance (p 0.001) was found among all BEEC subgroups comprising epispadias (E), classical exstrophy of the bladder (CBE) or cloacal exstrophy (CE), with male to female ratios of 1.4, 2.8, and 2.0, respectively. No association with parental age, maternal reproductive history or with periconceptional maternal exposure to alcohol, drugs, chemical noxa, radiation or infections was found. However, periconceptional maternal exposure to smoking (p 0.009) was significantly more common for CE patients than for the combined group of E/CBE patients. Only 16.8% of mothers followed the current recommendations

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of periconceptional folic acid supplementation. 17.6% had started supplementation before the 10th week of gestation. Interestingly, in the latter group, mothers of CE patients were more compliant (p 0.037) than mothers of the combined group of E/CBE patients. Furthermore, mothers of CE children knew significantly more often prenatally that their child would have a congenital malformation ($p < 0.0001$) than mothers of E/CBE children.

Conclusions—Our study corroborates the hypothesis that E, CBE and CE are causally related, representing a spectrum of the same developmental defect, with a small risk of recurrence within families. Embryonic exposure to maternal smoking appears to enforce the severity, whereas periconceptional folic acid supplementation does not seem to alleviate it. There is a disproportional prenatal ultrasound detection rate between severe and mild phenotypes, possibly due to the neglect of imaging of full urinary bladders with focus on neural tube defects.

Keywords

bladder exstrophy-epispadias complex; cloacal exstrophy; epidemiology; multifactorial inheritance

INTRODUCTION

The bladder exstrophy-epispadias complex (BEEC) represents a rare midline defect with variable expression ranging from isolated epispadias (E), and classic exstrophy of the bladder (CBE) to exstrophy of the cloaca (CE) which, in the latter case is commonly associated with omphalocele, spinal defects, and an imperforate anus.[1] BEEC develops around the fourth to sixth week of gestation, when the cloacal membrane is prematurely invaded by mesoderm in order to build the abdominal wall for the genitourinary system.[1] Timing of the rupture may determine the severity within the BEEC spectrum: if the membrane ruptures before the fourth week of gestation, CE ensues; if it ruptures after the urorectal septum has descended at six weeks, E or CBE occur.[1]

Among Europeans, the prevalence for E was estimated to be 2.4:100,000, as compared to 3.3:100,000 for CBE and 0.5:100,000 for CE.[2,3] According to the Birth Defects Monitoring Program of the Centers for Disease Control and Prevention (CDC), prevalence of CBE varies among North American ethnic groups. The highest rate of 8 per 100,000 was found in Native Americans, whereas Asians show the lowest rate of 1 per 100,000.[3] Indicating genetic determinants of BEEC, previous studies described a sex difference in population frequency for CBE between males and females of 1.5:1 to 5:1.[2] In the series of Shapiro et al., only affected females, the less frequently affected sex in the BEEC population, produced affected offspring,[4] suggesting a Carter effect, i.e. higher recurrence incidence in offspring of the less commonly affected sex.[5] Further evidence of genetic determinants is based on observations of occasional multiplex families, an increased recurrence risk for offspring of affected individuals and concordance rates in monozygotic and dizygotic BEEC twins.[4,6,7] Previous epidemiological studies have suggested a multifactorial mode of inheritance underlying BEEC.[2–4,6] However, non-genetic risk factors contributing to its etiology remain unknown. Aim of our survey was to identify non-genetic and genetic factors causally related to BEEC and to verify the current hypothesis that BEEC represents a spectrum of congenital anomalies. Based on the mechanism of dose related effects, a significant contribution of non-genetic risk factors should be revealed by comparing the milder phenotypes E and CBE with the more severe phenotype CE. Dose-related effects have been described for other known teratogenic agents, e.g. fetal alcohol syndrome where severity correlates with the amount of maternal alcohol use.[8]

PATIENTS AND METHODS

Study design was approved by the ethics committee of the University of Bonn and informed consent was obtained from patients and parents. 237 families with BEEC, contacted through various pediatric urology clinics and Austrian, German, Italian, Spanish and Swiss Bladder-Exstrophy Self Help Groups were invited to participate. Authors H. Reutter and H. Vogt are both engaged in the German (and H. Reutter also in the Spanish) self help support group and they were able, due to their personal engagement, to obtain data mainly from German and Spanish families. The epidemiological questionnaire, modeled according to Boyadjiev et al. [6], comprised 123 questions regarding family information, history of pregnancy, birth and environmental history and general health information. It was completed by 214 families. Partial clinical and past medical information was available for most consenting families.

Results were assessed statistically with SPSS 14 for Windows (SPSS 14.01, 2005, SPSS Inc, Chicago, IL). Comparison of male to female ratios to the expected 1 to 1 was assessed using a binomial test. To test for significance ($p < 0.05$) between BEEC subgroups, Fisher's Exact Test and Chi-Square Test were applied. For some results, the number of patients does not add up to 214, due to incompletely answered questionnaires.

RESULTS

Among the 214 families, E was diagnosed in 9% (n=19), CBE in 84% (n=180) and CE in 7% (n=15) of patients. Except for two Algerian and one Turkish family, all families were of European descent (Austrian n=9; British n=2; Croatian n=1; Dutch n=1; French n=2; German n=126; Italian n=9; Polish n=3; Rumanian n=1; Serbian n=1; Spanish n=46; Swiss n=10). The disparate distribution of patients amongst various European countries is due to sampling issues as defined in the Patients and Methods section. In addition to surgical evaluation and review of previous medical documentation, clinical genetic examinations were performed on 199 of the 214 BEEC patients. In two of the 214 families, BEEC re-occurred in a distant relative (third and fourth degree cousins, respectively).

A male predominance existed in all BEEC subgroups (E, CBE and CE) with male to female ratios of 1.4 (11/8), 2.8 (132/48) and 2.0 (10/5), respectively (table 1). The conducted ratio for the entire sample was 2.5:1 (153/61). Due to the overrepresentation of affected males in the CBE group (p 0.001) the gender difference for the entire sample was also significant (p 0.001). Consistent with the hypothesis that BEEC represents a clinical spectrum of the same developmental defect intermediate phenotypes existed in several patients. For differences regarding congenital anomalies or health problems outside the BEEC spectrum, we compared all three subgroups to each other, and the combined group of E and CBE patients to the group of CE patients without finding any difference (E/CBE 12.5% vs CE 11.6%). Here, dyslexia (n=9) and attention-deficit-hyperactivity-disorder (ADHD) were the most common (n=9), followed by cross psychomotor developmental delay (n=3), and cleft lip with or without cleft palate (n=2).

Regarding parental age as a risk factor, we assessed maternal (n=214) and paternal (n=214) age separately. Mean maternal age was highest with 30.0 years in the CBE group and 29.7 and 27.9, respectively, in the E and CE group. Mean paternal age was highest with 33.8 years in the E group and 32.7 and 31.4, respectively, in the CBE and CE group. Comparison of all groups with each other and the combined E/CBE group against the group of CE patients revealed no significant difference. Altogether, only two mothers were younger than 20 years.

Smoking (any amount) was reported by 30 out of 199 mothers (15%). Compared to the combined E/CBE group (185) we found significantly (161/24 versus 8/6; p 0.009) more CE patients (14) with exposure to first trimester maternal smoking (table 2). Exposure to alcohol

(any amount) was reported by 28 out of 199 women (14%), almost always limited to a few drinks before confirmation of pregnancy. None reported excessive drinking or a history of alcoholism. Periconceptional or first trimester intake of drugs or medication of any kind were limited to occasional intakes. Here, the intake of acetaminophen (n=17), acetylsalicylic acid (n=5), metoprolol (n=2), diazepam (n=2) and amitryptiline (n=2) was reported. Six percent of mothers (11 out of 194) reported periconceptional exposure to medical radiation (x-rays or CT-scans), albeit limited to a single application in all cases.

To address the issue of in vitro fertilization as a possible risk factor for BEEC, we analyzed the information on reproductive history available for 214 patients, including the total number of pregnancies, miscarriage history, assisted reproductive techniques and hormonal medications. Assisted reproduction, such as IVF and ICSI had been applied in three (1.4%) (twice ICSI and once IVF) of 214 mothers, resulting in the birth of two children with CBE and one child with CE. Of these mothers, 44 reported (21%) a history of, in all cases unique, spontaneous abortion. There was no significant difference compared with the rate of miscarriages in the E or CE group.

Only 16.8% of all mothers supplemented folic acid according to the current recommendations and a further 17.6% started before the 10^{th} week of gestation. Interestingly, among the mothers who started before the 10^{th} week of gestation, CE mothers were significantly (p 0.037) more compliant than mothers of the combined E/CBE group.

Further comparisons of the combined E/CBE group of patients and/or mothers with the group of CE patients and/or mothers revealed that mothers of CE patients had significantly more often diagnostic amniocentesis (164/15 versus 8/4; p 0.021) and, due to ultrasound, knew prenatally significantly more often that their child has a congenital malformation (170/15 versus 7/7; $p < 0.0001$) than mothers of E and CBE patients (table 3).

DISCUSSION

The current pathogenic concept of BEEC is based on the assumption of underlying polygenic gene-gene and multifactorial gene-environment interactions leading to a spectrum of anomalies in which part or all of the distal urinary tract fail to close and are exposed on the outer abdominal wall. Due to its low prevalence, epidemiological data on non-genetic risk factors are limited.[6] The present survey represents one of the largest to be conducted among BEEC families to date.

As described previously,[6] we also found a male predominance in all subgroups, significant for the CBE group and consecutively for the entire sample (p 0.001) (table 1). However, we were unable to reproduce earlier findings describing a sex ratio close to unity among CE patients,[6] but consistent with these also found some patients with an intermediate phenotype between the clinical entities of CBE and CE. In support of the assumption that all BEEC phenotypes (E, CBE and CE) share the same developmental defect, we failed to detect differences regarding the co-occurrence of congenital anomalies or health problems outside the BEEC spectrum.

Comparison of parental age in our BEEC families with the distribution in the general population was not performed since our families originated from 14 different countries. Contrary to previous findings describing an overrepresentation of very young mothers of BEEC children[2] but consistent with Boyadjiev et al.,[6] we only found two mothers younger than 20 years. Furthermore, we detected no differences in parental age among the different phenotypes. The two multiplex families observed suggest genetic components causally related to BEEC. However, pedigree structures are not compatible with Mendelian transmission, pointing towards polygenetic and/or environmental factors contributing to the risk.

Severe congenital anomalies occur in 5% of all live births among central Europeans, but the underlying causes of 65–75% of these defects remain unknown.[9] Multifactorial and polygenic malformations, e.g. cleft lip and/or cleft palate (CLP), spina bifida and congenital heart defects, generally carry an increased risk of recurrence for siblings (λs) of 1 in 20 to 1 in 30.[10] Regarding BEEC, Shapiro et al. having surveyed 2,500 CBE families in North America, found CBE to reoccur roughly in one of every 275 families.[4] Using these data for isolated CBE, a λs of 108 can be estimated based on an overall prevalence of CBE among Europeans with 1 in 20,000 to 1 in 30,000 live births,.[4] Therefore, the risk is 108-times higher compared to the general population (risk comparison λs: 1/275 divided 1/30,000 = 108). Furthermore, in their series, Shapiro et al. described a 400-fold increased risk in offspring of affected individuals (λo) compared to the general population.[4] These data were confirmed by concordance rates among mono- and dizygotic BEEC twins.[7]

Ascertainment of possible teratogenic exposures was limited by sample size and lack of an available control group. Looking at our complete sample, we noticed the same frequency (15%) of first trimester fetal exposure to maternal smoking as recently observed.[6] However, comparing the different subgroups, first trimester exposure to maternal smoking was found to be associated with formation of the more severe BEEC phenotype (p 0.009) possibly indicating gene-environment interactions as described by Maestri et al. who reported that the risk of non-syndromic oral clefts was significantly influenced by an interaction involving genetic variants of the *TGFB3*-gene and first trimester exposure to maternal smoking.[11]

Exposure to alcohol (any amount) was reported by 14% of mothers, almost always limited to a few drinks before confirmation of pregnancy. A detailed study by the CDC found an alcohol exposure rate in the general population of 12.8% among women who delivered in 1999, parallel to our present survey.[12] Also, in our study report of exposure to periconceptional or first trimester receipt of drugs or medications these were limited to few occasions. It has been scientifically proven that under regular use, none of the substances reported possesses teratogenic effects.[13] Exposure to medical radiation (x-rays or CT-scans) was reported in 6% of mothers, all cases limited to a single application. The Israel Teratogen Information Service reported a value of 10.9% of X-ray exposures during early pregnancy in a ten year prospective study which comprises almost twice the rate compared to our cohort.[14] However, they did not observe any increased prevalence of birth defects in the outcome follow-up. Other studies concluded that nuclear medicine and radiological diagnostic procedures, if not repeated during pregnancy, do not exceed 100 mSv, the threshold dose for deterministic effects on the fetus.[15]

A previous report suggested a possible association between in vitro fertilization and BEEC.[16] In our study, assisted reproduction, such as IVF and ICSI had been applied in 1.4% (twice ICSI and once IVF) of mothers resulting in the birth of two children with CBE and one child with CE. In 2000, the combined rate of newborns resulting from IVF or ICSI procedures in Germany was 1.3%, suggesting that IVF and ICSI do not carry a major risk of BEEC formation.[17]

Forty-four of the 214 (21%) mothers reported a history of, in all cases unique, spontaneous abortion reflecting the observation by Buss et al. who, during follow-up of pregnancies in a large Danish cohort, found a value of 20.9%.[18] Unlike previous observations of a significantly greater rate of miscarriages among mothers of E patients (n=10; 34%), we found the highest rate in the CBE group (n=37; 18.6%).[6]

Periconceptional folic acid supplementation implemented according to the current recommendations has been beneficial in the prevention of neural tube defects (NTDs), and it has been assumed to be preventative in the occurrence of non-syndromic omphalocele.[19] Both

these congenital anomalies are part of the BEEC spectrum. In our survey, only 16.8% of mothers had supplemented folic acid starting before conception and only 17.6% of all mothers started before the 10th week of gestation. Interestingly, mothers of children with CE were significantly (p 0.037) more compliant in their supplementation starting before the 10th week of gestation than mothers of the combined group of E/CBE patients. This contradicting finding might either be due to the fact that NTDs and omphalocele are only in part receptive to the preventive effects of periconceptional folic acid and/or that beneficial effects only display if supplementation has been started before conception according to the current recommendations. On the other hand NTDs and omphalocele associated with BEEC might underlie a completely different pathogenic concept compared to their isolated occurrence.

Further comparisons of patients and/or mothers of the combined E/CBE group with patients and/or mothers of the CE group revealed that mothers of CE patients underwent prenatal diagnostic amniocentesis significantly (p 0.021) more often and prenatally, were significantly ($p < 0.0001$) more often aware of their child being affected by major congenital malformation than mothers of E/CBE patients (table 3). In general, due to better prenatal ultrasound techniques, BEEC has been diagnosed prenatally more frequently than in the past. However, most prenatal reports describe detection of fetuses with CE, due to the severity and the high frequency of NTDs associated with this phenotype.[20] The disproportion of barely diagnosed milder but much more prevalent BEEC phenotypes could be due to the fact that prenatal ultrasound focuses more on imaging of NTDs than on the full urinary bladder.

CONCLUSIONS

Data ascertained from a retrospectively administered questionnaire are potentially inaccurate and recall biases that may have affected data collection from mothers in the epidemiological questionnaire. However, the present survey could not only confirm previous data but also raises the question whether maternal smoking contributes to phenotypic severity of BEEC, and whether periconceptional folic acid supplementation could potentially alleviate it. Nonetheless, we acknowledge the limited size of our sample and that further prospective investigations of larger study cohorts are necessary to corroborate or reject the findings.

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Abbreviations

BEEC
: bladder exstrophy-epispadias complex

CBE
: classical exstrophy of the bladder

CE
: cloacal exstrophy

E
: isolated epispadias

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Table 1

Sex distribution of the complete sample

Diagnosis	patients (n)	males (n)	(%)	females (n)
Epispadias (E)	19	11	5.1	8
Classical Bladder Exstrophy (CBE)	180	132	61.7	48
Cloacal Exstrophy (CE)	15	10	4.7	5
Total	214	153	71.5	61

Table 2

Intrauterine first trimester exposure to smoking

	exposure to smoking			
	no exposure	**exposure**	**(%)**	***p*-value**
E and CBE patients	161	24	13	
CE patients	8	6	43	
				0.009

Table 3

Prenatal pregnancy monitoring

	Prenatal pregnancy monitoring		
	diagnostic amniocentesis (Yes/No)	**prenatal diagnosis of congenital malformation (Yes/No)**	***p*-values**
E and CBE patients	165/15	170/15	0.021
CE patients	8/4	7/7	0.0001