Association Between Exstrophy-epispadias Complex And Congenital Anomalies: A German Multicenter Study

Anne-Karoline Ebert, Nadine Zwink, Ekkehart Jenetzky, Raimund Stein, Thomas M. Boemers, Martin Lacher, Caroline Fortmann, Florian Obermayr, Margit Fisch, Kiarasch Mortazawi, Eberhard Schmiedeke, Volker Eisenschmidt, Mattias Schäfer, Karin Hirsch, Wolfgang H. Rösch, and Heiko Reutter

OBJECTIVE To further investigate associated anomalies in exstrophy-epispadias complex (EEC) patients congenital uro-rectal malformations network (CURE-Net) database was systematically screened. In literature the EEC comprises a spectrum of anomalies, mainly occurring "isolated" without additional congenital defects. Nevertheless, previous epidemiological studies indicated a higher association with renal, anorectal, and lower neurotubular anomalies, which may originate from the same developmental morphogenetic fields.

MATERIALS AND METHODS Seventy-three prospectively (born since 2009) and 162 cross-sectional recruited EEC patients (born 1948-2008) were analyzed. Associated anomalies were derived from patient's medical data as well as from a physical examination during a physician's interview, classified according to the international statistical classification of diseases and related health problems and grouped with the London Dysmorphology Database. Descriptive statistical analyses were performed.

RESULTS Majority of participants were male (68%) and expressed the classical bladder exstrophy phenotype (71%). Exstrophy variants occurred significantly more often in newborns (21%, $P < .0001$). Anomalies such as inguinal hernias, skeleton, and joint anomalies were equally present in both groups ($P = .65$ and $P = .67$). Heart defects were seen more often in newborns (6%) than in the cross-sectional group (1%; $P = .033$) and the general German population (1%). In total, 59% of the prospective and 48% of the cross-sectional patients had associated anomalies outside the spectrum ($P = .16$).

CONCLUSION Phenomenological multicenter data confirmed the dimension of associated anomalies inside and outside the EEC spectrum. The detected anomalies are either important in preparing for the primary reconstruction or later in long-term follow-up. Associated anomalies of EEC should be spotlighted during routine check-up in all EEC patients. UROLOGY 123: 210–220, 2019.

Funding Support: *This work was done in the context of the "Network for Systematic Investigation of the Molecular Causes, Clinical Implications and Psychosocial Outcome of Congenital Uro-Rectal Malformations (CURE-Net)" and supported by a research grant (01GM08107) from the German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung, BMBF) 2009-2012. Statistical calculations are supported by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG), funding signs JE681/3-1 (2013-2015), EB521/2-1 and JE681/4-1 (2015-2018). HR was supported by a grant from the DFG (RE 1723/1-1).* http://www.cure-net.de.

Financial Disclosure: *The authors declare that they have no relevant financial interests.*

From the Department of Pediatric Urology, University Hospital for Urology and Pediatric Urology Ulm, Ulm, Germany; the Department of Child and Adolescent Psychiatry, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany; the Child Center Maulbronn GmbH, Hospital for Pediatric Neurology and Social Pediatrics, Maulbronn, Germany; the Department of Pediatric and Adolescent Urology, University of Mannheim, Mannheim, Germany; the Department of Pediatric Surgery and Urology, University Hospital Cologne, Cologne, Germany; the Department of Pediatric Surgery, University of Leipzig, Leipzig, Germany; the Center of Pediatric Surgery Hannover, Hannover Medical School and Bult Children's Hospital, Hannover, Germany; the Department of Pediatric Surgery and Urology, University Hospital for Child and Adolescent Medicine Tübingen, Tübingen, Germany; the Department of Pediatric Urology, University Hospital Hamburg-Eppendorf, Hamburg, Germany; the Department of Pediatric Surgery, Städtisches Klinikum Karlsruhe, Karlsruhe, Germany; the Department of Pediatric Surgery and Urology, Center for Child and Youth Health, Klinikum Bremen-Mitte, Bremen, Germany; the Department of Pediatric Urology, University Medical Center Regensburg, Regensburg, Germany; the Department of Pediatric Surgery and Urology, Cnopf'sche Kinderklinik, Nürnberg, Germany; the Department of Pediatric Urology, University Hospital Erlangen, Erlangen, Germany; the Institute of Human Genetics, University of Bonn, Bonn, Germany; and the Department of Neonatology and Pediatric Intensive Care, Children's Hospital, University of Bonn, Bonn, Germany

Address correspondence to: Heiko Reutter, Ph.D, M.D., Department of Neonatology and Pediatric Intensive Care and Institute of Human Genetics, University of Bonn, Sigmund-Freud-Str. 25, Bonn 53105, Germany. E-mail: reutter@uni-bonn.de

Submitted: April 5, 2018, accepted (with revisions): May 8, 2018

 https://doi.org/10.1016/j.urology.2018.05.039
0090-4295

Comprehensive understanding of the exstrophy-epispadias complex (EEC) is still most challenging in pediatric urology. Today, due to a better clinical understanding and the growing awareness of a more accurate phenotype description, a higher association of vascular, cardiac, chromosomal, musculoskeletal anomalies, anorectal malformation, and cleft lip and/or palate is reported with various EEC phenotypes.[1-11] The majorities of previously associated anomalies, such as renal and lower neurotubular anomalies, are nowadays acknowledged to be a genuine part of the EEC spectrum.[3-6] Exemplary, previous reports describe malformations of the upper urinary tract in up to one-third of patients.[12] In accordance, the upper and lower urinary tract, as well as the lower neurotubular part, originate of the same developmental morphogenetic field rendering a co-occurrence of defects in the respective organ system likely.[13] A British epidemiological study based on data from the Northern Perinatal Mortality Survey defined 31% of their collected EEC cases to be "non-isolated" due to either additional structural or chromosomal anomalies, including only previously described associated anomalies.[3] Beyond previous reports, a systematic and comprehensive phenomenological investigation of a large nationwide EEC cohort would further enlighten the knowledge about associated anomalies. Therefore, the database of the multicenter German-wide Network for Congenital Uro-REctal malformations (CURE-Net) was used to systematically report associated anomalies in EEC in a structured way.

MATERIALS AND METHODS

Study Population

CURE-Net (www.cure-net.de) was established in 2009. Cases with EEC are identified and recruited through participating departments of pediatric urology and pediatric surgery throughout Germany and the 2 German self-help organizations Blasenekstrophie/Epispadie e.V. (www.blasenekstrophie.de) and Kloakenekstrophie e.V. (www.kloakenekstrophie.de). The CURE-Net register has a centralized database comprising clinical data of a prospective cohort with patients approximately 1 year old at the time of data acquisition and a cross-sectional cohort of older EEC individuals. In the prospective cohort 1 main focus lay on collection of epidemiologic data via parent and physician questionnaires. Primary focus of the cross-sectional study was the assessment of medical records to get an overview of treatment strategies over the past years in Germany, with an emphasis on short- and long-term outcome issues. The database was in principle used to collect as much information on EEC individuals as possible. Therefore, there were no exclusion criteria for EEC patient recruitment.

Data Retrieval

For a standardized description of EEC phenotypes the international classification by Gearhart & Jeffs[12] was used. Documentation of associated anomalies according to the international statistical classification of diseases and related health problems (ICD-10) was based on the patients' charts and coequally on the physicians' physical investigation at the time of interview. Recruitment was done by 4 independent CURE-Net physicians, 2 of them were pediatrician and geneticists, the others had specified for pediatric urology and pediatric surgery.

Associated anomalies were grouped according to the London Dysmorphology Database (LDD).[14] In literature, anomalies of the urinary tract, the abdominal wall such as omphalocele, musculus rectus, and pelvic diastasis, the lower spine and lower neurotubular defects, the anus, renal anomalies, and the genitalia such as bipartite clitoris are included in the EEC spectrum. These EEC cases were therefore defined "isolated." However, single additional anomalies, which were only minor or simple signs of dysmorphism were not subsumed under co-occurring anomalies and therefore called "non-isolated". Among these minor signs of dysmorphism we classified for instance vertebral scoliosis, patent or persistent foramen ovale (PFO), ear anomalies (accessory auricular appendage and/or preauricular tag, unspecified, and minor malformation of the auricle, low set ears), clinodactylie, anomalies of the skin, and skin appendages.

Written informed consent was obtained from all patients older than 18 years and the parents of affected minors. This study was approved by each participating center's Institutional Ethics Committee (eg, University of Regensburg No. 09/053, University of Ulm No. 425/13).

Statistical Analysis

Descriptive data of the study population and associated anomalies are presented in absolute and relative frequencies. To assess possible differences between the prospective and cross-sectional patient group or between the different EEC phenotypes, Fisher's exact test was used. Frequencies of associated anomalies were compared to the German population, such as data from the German Competence Network for Congenital Heart Defects (http://www.kompetenznetz-ahf.de/en/home/). Statistical significance was defined by $P < .05$. Analyses were performed by the statistics software SAS, version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Patients´Characteristics

Data of 73 prospective EEC patients (median age 1 year; 68% males; 63% classical bladder exstrophy [CBE]) born between January 2009 and April 2016 and 162 cross-sectional EEC patients (median age 14 years; 68% males; 75% CBE) were included in this analysis (Table 1). Exstrophy variants, however, were overrepresented in the prospective group with 21% in comparison vs 4% in the cross-sectional group ($P < .0001$). Upper and lower fissures were seen in up to 10% in the prospective cohort and this is a much higher proportion than in the cross-sectional cohort (Table 1). In the prospective group 3 of 15 (20%) and in the cross-sectional group 4 of 7 of the exstrophy variants were female (57%). The overall male-to-female ratio in the prospective group was 2.2:1, with a male-to-female ratio of 1.6:1 for CBE and 4.0:1 for epispadias (E). In the cross-sectional cohort the overall male-to-female ratio was 2.1:1, 2.5:1 for CBE, 1.9:1 for E, and for cloacal exstrophy (CE) 1.3:1. Due to the retrospective data acquisition missing values only occurred in cross-sectional patients (3%).

Associated Anomalies

Associated anomalies outside the EEC spectrum were reported in 43 (59%) of the prospective and 78 (48%) of the cross-sectional patients ($P = .16$). Although, numbers of included CE patients

Table 1. Characteristics of the study population (N=235)

	Newborn Group (N = 73)	Cross-Sectional Patient Group (N = 162)
Gender		
Female	23 (32%)	52 (32%)
Male	50 (68%)	110 (68%)
Male-to-female ratio	2.2: 1	2.1: 1
Age at the time of data acquisition		
Median (IQR)	1 (0-1) yrs	14 (7-21) yrs
Min; Max	0; 4 yrs	2; 62 yrs
Phenotype		
Classical bladder exstrophy	46 (63%)	121 (75%)
Epispadias I	1 (1%)	3 (2%)
Epispadias II	1 (1%)	2 (1%)
Epispadias III	8 (11%)	18 (11%)
Cloacal exstrophy	2 (3%)	7 (4%)
Other exstrophy variant	15 (21%)	7 (4%)
Upper vesical fissure	7 (10%)	2 (1%)
Lower vesical fissure	7 (10%)	1 (1%)
Covered exstrophy	1 (1%)	2 (1%)
Duplicated exstrophy	0	0
Pseudoexstrophy	0	1 (1%)
Others	0	1 (1%)
Missing value	0	4 (3%)

IQR, interquartile range.

in both cohorts were small, anomalies outside and inside the spectrum affected in the first instance CE patients. E and CBE patients, however, showed anomalies in the "inside spectrum" body areas, such as uro-genital and gastrointestinal tract, and the "outside spectrum" body areas, such as brain, heart, abdomen, skeleton, joints, skin, and chromosomal abnormalities or syndromes (Tables 2 and 3).

Associated Anomalies Within the EEC Spectrum (Table 2)

Renal anomalies occurred nearly in the same proportion in the prospective and the cross-sectional patients' groups (18% vs 17%; P = .31). Forty-six percent of the prospective patients (N = 6), 4 of them having CBE and 1 each of E or exstrophy variants phenotype, had vesicoureteral reflux documented. One prospective patient each had an ectopic ureter and renal dysplasia, 2 had a duplex kidney (15%). In the cross-sectional group, vesicoureteral reflux was reported in 15%, all of them had CBE (N = 3). Three patients had a duplex kidney (15%), 2 further had a pelvic and fusion kidney (10%), and 1 patient each had renal hypoplasia and renal function impairment due to renal scaring (5%). Renal anomalies were reported across all EEC phenotypes. The majority of patients with a renal abnormality had the CBE phenotype (prospective patients 62%, cross-sectional patients 80%) and were males (prospective patients 69%, cross-sectional patients 60%).

Genital anomalies other than E were described, even when not statistically significant, more commonly seen in the prospective than in cross-sectional patients (18% vs 9%; P = .061). Stratification for gender showed that genital anomalies almost exclusively occurred in males (prospective patients: N = 13, 100%; cross-sectional patients: N = 11, 73%). Affected prospective patients had mainly EEC variants (N = 8, 62%), followed by CBE (N = 4, 31%). Affected cross-sectional patients had mainly CBE (N = 10, 67%). Cryptorchidism was found in the same extent in the prospective (N = 3, 23%) and the cross-sectional patients (N = 3, 20%), respectively. Two prospective males had penile duplication (15%), 1 a penile agenesia (8%) and 2 a scrotum bipartitum (15%). In the cross-sectional patient group 1 patient each had a buried penis (7%) and a penoscrotal transposition (7%). Cross-sectional female patients had a uterus duplex twice (13%) in CE and CBE, and 1 vagina duplex (7%) in CBE.

Abdominal anomaly: Prospective patients with omphalocele were all male, and the majority were found in the cross-sectional patient group (60%). All of them had coincidental inguinal hernias. Among them, subgroup analyses showed 3 of the prospective patients having CBE (60%) and 1 patient each with CE and an exstrophy variant. In the corresponding cross-sectional patient group, omphalocele was mainly reported in CE patients (n = 4, 80%) and once in an exstrophy variant.

Associated Anomalies Outside the EEC Spectrum

Detailed associated anomalies outside the EEC spectrum are presented in Table 3. Anomalies of the skeleton and joints were reported frequently in the prospective cohort (38%), such as single joint hyperextensibility, vertebral and bone anomalies, followed by abdomen anomalies (36%). In the cross-sectional patient group, skeleton and joint anomalies were documented in 42%, abdominal anomalies in 32%. The following diagnoses were reported: butterfly vertebra, hemivertebra, scoliosis, coxa valga, finger joint hyperextensibility, club foot, and pigeon toes. Inguinal hernias were subsumed to the LDD category "abdomen" and were reported in 26 (36%) of the prospective and in 52 (32%) of the cross-sectional patients respectively (P = .65). Inguinal hernias occurred almost exclusively in males (prospective patients 65%, cross-sectional patients 90%) and mainly in CBE patients (prospective

Table 2. Associated anomalies in patients in the EEC spectrum according to diagnostic subgroups

	Newborn Patient Group					Cross-Sectional Patients				
	All (N = 73)	CBE (N = 46)	E (N = 10)	CE (N = 2)	OtherVariants (N = 15)	All* (N = 162)	CBE (N = 121)	E (N = 23)	CE (N = 7)	Other Variants (N = 7)
Kidney	13 (18%)	8 (17%)	1 (10%)	2 (100%)	2 (13%)	20 (17%)	16 (13%)	2 (9%)	2 (29%)	0
Genital	13 (18%)	4 (9%)	0	1 (50%)	8 (53%)	15 (9%)	10 (8%)	3 (13%)	1 (14%)	1 (14%)
Central nervoussy stem *(spina bifida, hydrocephaly, microcephaly)*	1 (1%)	0	0	1 (50%)	0	3 (2%)	0	0	3 (43%)	0
Gastrointestinal *(anal atresia/stenosis)*	1 (1%)	1 (2%)	0	0	0	2 (1%)	1 (1%)	0	0	1 (14%)

CBE, classical bladder exstrophy; E, epispadias; CE, cloacal exstrophy.
* Including 4 patients with missing information on phenotype.

patients 48%, cross-sectional patients 36%). All documented heart defects occurred more frequently in prospective cohort compared to the cross-sectional patient group (18% vs 2%; $P < .0001$). Among the affected prospective patients—the majority was male (69%)—6 had a CBE, 4 an exstrophy variant, 1 a CE, and 2 E. However, possible transient and therefore physiologic diagnoses were excluded for final analysis, such as persistent foramen ovale (PFO) in 4 patients younger than 9 months, a persistent ductus arteriosus (PDA) in 1 patient with 6 months and further 2 patients with both PFO and PDA younger than 4 months. Two E patients were marked to have any cardiac anomalies but with unknown ICD-10 specification. Relevant cardiac anomalies were found in 4 prospective patients (6%). A 1 month old CBE patient had a combined atrial and ventricular septal defect (ASD+VSD). One CE and 2 CBE patients had a VSD. In the cross-sectional cohort, 4 patients, all with CBE and 50% male, being 10, 11, 16, and 24 years of age at time of data retrieval, had cardiac anomalies documented such as PFO (n = 2), PDA, and ASD II (ASD secundum type) (each n = 1). According the prospective cohort, potentially physiological cardiac anomalies were excluded, as their persistence beyond the first year of life was not proven. So, only 1 cross-sectional patient with ASD II was included in the final analysis (1%).

Chromosomal anomalies, monogenic disorders, and syndromic appearances were equally present in both cohorts (3%). In the prospective group 1 patient had Down syndrome, 2 patients had an Opitz BBB/G-Syndrome with 1 child having CBE and 1 having E. In the cross-sectional patients, 2 individuals showed developmental delay, 1 blepharophimosis syndrome, 1 microdeletions syndrome 22q11, 1 ADHS syndrome, with 3% of the CBE, and 14% of the CE patients. None of the E or EEC variants patients were affected.

Further associated disorders: Endocrine and hematologic abnormalities were exclusively found in the cross-sectional group in 3%. These disorders do not seem associated but rather sporadic and random. Due to their predilection at a later age, 2 patients, 14 and 27 years old, were diagnosed with hypothyroidism and 1 with Hashimoto thyroiditis. One boy, whose biological mother was drug-dependent, had a Hepatitis C.

DISCUSSION

The current comprehensive analysis of the large nationwide CURE-Net database enhances the general knowledge about the diversity of associated anomalies in EEC, as a widespread range of associated anomalies was detected, to our best knowledge, not described in literature to this extent before (Table 4). As expected, in the 2 CURE-Net cohorts—prospective and cross-sectional patients—male-to-female ratio were comparable to literature.[1-4] Nearly all previous series found a predominance of the male gender, however, the reason for this is still unclear. Due to the lack of mandatory reporting to a centralized birth register and the numbers of pregnancies terminated before birth in Germany, no further valid data are available on this specific epidemiological topic. Phenotype distribution within the EEC spectrum showed as expected, CBE predominant in both cohorts and all E occurring with a nearly equal rate of 14%. However, not described to this extent before, exstrophy variants were

Table 3. Associated anomalies in patients outside EEC spectrum according to diagnostic subgroups

	Newborn Patient Group					Cross-Sectional Patients				
	All (N = 73)	CBE (N = 46)	E (N = 10)	CE (N = 2)	Other Variants (N = 15)	All* (N = 162)	CBE (N = 121)	E (N = 23)	CE (N = 7)	Other Variants (N = 7)
Anatomy	2 (3%)	0	0	1 (50%)	1 (7%)	10 (6%)	4 (3%)	3 (13%)	3 (43%)	0
Body structure	0	0	0	0	0	4 (2%)	1 (1%)	1 (4%)	2 (29%)	0
Skull in general	0	0	0	0	0	1 (1%)	1 (1%)	0	0	1 (14%)
Forehead region	1 (1%)	0	0	0	1 (7%)	0	0	0	0	0
Cervical structure	0	0	0	0	0	0	0	0	0	0
Brain	1 (1%)	1 (2%)	0	0	0	1 (1%)	0	0	1 (14%)	0
Hair	0	0	0	0	0	1 (1%)	1 (1%)	0	0	0
Eyes, orbita	3 (4%)	0	0	1 (50%)	2 (13%)	10 (6%)	8 (7%)	0	2 (29%)	0
Ear nose and throat	2 (3%)	0	0	1 (50%)	1 (7%)	2 (1%)	2 (2%)	0	0	0
Face	2 (3%)	0	0	1 (50%)	1 (7%)	4 (2%)	3 (2%)	0	1 (14%)	0
Thorax	0	0	0	0	0	3 (2%)	2 (2%)	0	1 (14%)	0
Lung, trachea	1 (1%)	0	0	0	1 (7%)	1 (1%)	1 (1%)	0	0	0
Oesophagus	0	0	0	0	0	2 (1%)	0	0	2 (29%)	0
Heart	4 (6%)	3 (7%)	0	1 (50%)	0	1 (1%)	1 (1%)	0	0	0
Abdomen	26 (36%)	23 (50%)	0	1 (50%)	2 (13%)	52 (32%)	42 (35%)	3 (13%)	5 (71%)	2 (29%)
Gastrointestinal tract	5 (7%)	3 (7%)	1 (10%)	1 (50%)	0	11 (7%)	3 (2%)	1 (4%)	6 (86%)	1 (14%)
Extremities	1 (1%)	0	0	0	1 (7%)	2 (1%)	0	0	2 (29%)	0
Skeleton, joints	28 (38%)	21 (46%)	0	2 (100%)	5 (33%)	68 (42%)	55 (45%)	3 (13%)	6 (86%)	4 (57%)
Muscles	1 (1%)	0	0	1 (50%)	0	2 (1%)	0	0	2 (29%)	0
Skin	2 (3%)	1 (2%)	1 (10%)	0	0	13 (8%)	10 (8%)	2 (9%)	1 (14%)	0
Endocrine disorders	0	0	0	0	0	5 (3%)	3 (2%)	0	0	2 (29%)
Chromosomal abnormality/syndrome	2 (3%)	1 (2%)	1 (10%)	0	0	5 (3%)	4 (3%)	0	1 (14%)	0
Hematological diseases	0	0	0	0	0	1 (1%)	1 (1%)	0	0	0
Others	1 (1%)	1 (2%)	0	0	0	2 (1%)	0	1 (4%)	1 (14%)	0

CBE, classical bladder exstrophy; E, epispadias; CE, cloacal exstrophy.
* Including 4 patients with missing information on phenotype.

Table 4. Congenital anomalies in patients with EEC: Literature review

Study	Database	Index Cases	Code	Time Period	Phenotype	Associated Anomaly In Spectrum	Anomalies Outside Spectrum
Nelson et al, 2005[1]	Nationwide Inpatient Sample (NIS).	205 of 9,452,110 newborns	ICD-9	1988-2000	Not specified, "bladder exstrophy"	Lower gastrointestinal anomalies 19.3 (OR (95%CI) 188.6 (162-219))	Vascular anomalies 4.6 (OR (95%CI) 4.4 (3.3-5.8)
	United States					Preterm birth 17.5 (OR (95%CI) 3.0 (2.5−3.5))	Cardiac anomalies 3.4 (OR (95%CI) 4.5 (3.2-6.3)
							Chromosomal anomalies 1.1 (OR (95%CI) 7.7 (4.3-13.6))
						Orthopedic anomalies 13.2 (OR (95%CI) 13.1 (11.0 −15.6))	Cleft lip and/or palate 1.1 (OR (95%CI) 8.0 (4.4-14.3))
						Spina bifida 6.8 (OR (95%CI) 224.3 (177 −284))	
Jayachandran et al, 2011[3]	Northern congenital abnormality survey, Northern England	43 of 824,368	WHO International Classification of Diseases,10th revision.	1995-2008	BEEC: 24 CBE, 13 E, 6 CE;	Gastrointestinal (gastroschisis, exomphalos, diaphragmatic	Cardiac (ventricular septal defect, atrial septal defect, Fallot's tetralogy, pulmonary stenosis)
					EEC isolated 69%, "non-isolated" 31%	hernia, anal atresia/ stenosis) 9 (21%)	7 (16.3%)
							Musculoskeletal (arm reduction defects, arthrogryposis, sacral agenesis) 4 (9.3%)
						Urinary system 4 (9.3%)	

Continued

Table 4. Continued

Study	Database	Index Cases	Code	Time Period	Phenotype	Associated Anomaly In Spectrum	Anomalies Outside Spectrum
						Central nervous system (spina bifida, anencephaly, microcephaly) 6 (14%)	Chromosomal/ other 3 (7%)
						29 (69%)	
Reutter et al, 2011[2]	European study cohort,	441	National	ES:2003-2008	ES: 21 (13%) E, 130 (78%) CBE, 15 (9%) CE		Down syndrome 3/441 (0.68%) (OR (95%CI) 6.10 (2.08-17.77))
	NAS group		Birth Defect Prevention Study questionnaire of the U. S. Centers of Disease Control and Prevention	NAS: 2001-2005	NAS: 22(8%) E, 236 (86%) CBE,16 (6%) CE		Ventricular septal defect 5/438 (1.14%) (OR (95%CI)4.47 (1.91-10.36)) CL-P 3/438 (0.68%) (OR (95%CI) 7.98 (2.72-23.25))
Cervellione et al, 2015[4]	European study cohort (ESPU driven, 27 European countries)	238	116 National investigators: response rate 79%	2010	71 E (67 males),	General associated anomalies	Down syndrome 1/ 146 (0.7%) CBE, 1/21 (4.8%) CE
					CBE 146 (97 males; 2 female with exstrophy variant)	E 2/71 (2.8%), CBE 8/146 (5.5%), CE	Genetic 1/71 (1.4%) E
					CE 21 (17male)	15/21 (71.4%)	Cardiac 1/146 (0.7%) CBE, 2/ 21 (10%) CE
						In detail: ARM 2/146 (1.4%) CBE Orthopedic 2/21 (10%) CE CNS 5/21 (24%) CE	

Continued

Table 4. Continued

Study	Database	Index Cases	Code	Time Period	Phenotype	Associated Anomaly In Spectrum	Anomalies Outside Spectrum
						Urinary 1/71 (1.4%) E, 1/146 (0.7%) CBE	
Current study	CURE-Net	235 (73 newborns, 162 cross-sectional cohort)	ICD-10, London Dysmorphology Database	2009-April 2016	Newborns: 46 (63%) CBE, 10 (13%) E, 2 (3%) CE, 15 (21%) variants; Cross-sectional patients: 121 (75%) CBE, 23 (14%) E, 7 (4%) CE, 7 (4%) variants; Newborns 41% and cross-sectional patients 52% isolated EEC (p=0.16)	Newborn/cross-sectional: Urinary 13 (18%) / 20 (17%) Genital 14 (19%) / 15 (9%) CNS 1 (1%) / 3 (2%) Gastrointestinal (ARM/ anal stenosis) 1 (1%)/ 2 (1%)	Anomalies (newborn/cross-sectional): - abdominal (hernias) 26 (36%)/ 52 (32%), - skeleton and joint 28 (38%) / 68 (42%) - cardiac 4 (6%) / 1 (1%) - genetic 2 (3%) / 5 (3%)

seen with an unexpected and significant high incidence of 21% in this prospective EEC group compared to the cross-sectional cohort ($P < .0001$). The reason for this finding is unknown and needs a confirmation with a larger cohort. However, it can be hypothesized that exstrophy variants may generally be subsumed in the CBE phenotype, especially in retrospective observations. In the prospective study of Cervellione et al only a minor proportion of exstrophy variants was found in a group of the 49 female CBE (n = 2; 4%).[4]

Most individuals with EEC do have additional anomalies. To discuss this issue adequately, we must distinguish between anomalies included in the EEC spectrum and additionally other coincidental ones. Most recently, it was confirmed that urinary tract anomalies may occur up to 1.6-9.1 times more often in EEC than in general population, depending on the EEC phenotype.[5,6] In the Hopkins' database of 1,044 EEC patients, 2.8% of 462 included EEC patients had concomitant renal anomalies.[6] For a large CE cohort, Suson et al reported urinary tract anomalies being predominant in 60% of affected males.[5] Female CE individuals were additionally affected with Müllerian duct anomalies in 65.7% such as uterine or vaginal duplication, obstruction, and/or absence. Females with abnormal Müllerian anatomy had 10 times more often renal abnormalities than the not affected.[5] In the CURE-Net cohorts associated urogenital anomalies were reported quite equally distributed for prospective and the cross-sectional patients. The prospective CBE were predominately affected with renal anomalies (N = 8, 62%), in the cross-sectional cohort CBE 80% (N = 16). As however, renal anomalies might have clinical significance, a postnatal renal ultrasound should be obligatory to detect these abnormalities sufficiently in detail and is for sure the clinical standard in preparing for the initial closure worldwide.

In CURE-Net cardiac comorbidity was higher in the prospective group compared to the cross-sectional group (6% vs 1%; $P = .033$) and to the German normal population (1%).[15] The epidemiological study by Jayachandran et at in 2011 found 16.7% cardiac anomalies such as VSD, ASD, Fallot's Tetralogy, and pulmonary stenosis in 43 EEC individuals not differentiating between their phenotypes.[3] A similar finding was also detected in a large European cohort but very carefully and critically discussed, however, most recently confirmed again by a major EEC center in Germany.[2,9] In the German competence network for congenital heart defects based on the results of 260 participating institutions a congenital heart disease prevalence of 107.6 per 10,000 live births was estimated.[15] Although, the initial reported incidence of cardiac anomalies documented in the standardized manner in the present EEC cohort was 18% for the prospective group, the relevance of the described cardiac defects such as persistent PDA and PFO were overestimated and related to the young age at presentation. Therefore, these physiological and not hemodynamic relevant findings were excluded, usually possibly present in up to 25% of a healthy population. The incidence of congenital heart disease in the cross-sectional resembles the rate of the general German population (http://www.kompetenznetz-ahf.de/en/home/). Some centers might detect more physiologic and young age-related abnormalities, as they perform a mandatory preoperative cardiac investigation since some years of growing awareness. Associated cardiac anomalies, however, should be documented and taking into consideration when planning major surgery in a hemodynamic instable and vulnerable period of life. Therefore, an echocardiographic evaluation before EEC reconstruction would be highly desirable.

It is well known that the considerable amount of approximately 15% to 20% of healthy newborns have 1 minor anomaly and in addition a 3% risk of associated major abnormalities.[16] The systematic investigation of the prevalence of associated anomalies in EEC showed that 43 (59%) prospective and 78 (48%) cross-sectional patients had associated anomalies outside the spectrum. Jayachandran et al found 31% of their EEC cohort to be associated with further anomalies, some even with several major abnormalities.[3] As the rate of associated anomalies outside the spectrum in this study is considerably higher than described in literature before, associated anomalies should be assessed more thoroughly when describing the current EEC phenotype of our EEC patients in future.

Strengths and Limitations

Strength of this study is the large, multicenter, and population-based patient recruitment throughout Germany. A known precondition of the comparison of data from a historical and contemporary group is considerable systematic considerations. However, most collected items were congruent in both EEC cohorts. Anomalies grouped by the LDD were additionally cross-checked with the reported ICD-10 diagnoses, if available, to improve data accuracy. Unfortunately, the completeness of medical records in the cross-sectional patient group was not always given. Therefore, an underestimate of some anomalies cannot be excluded in this group. According to a recent study assessing the incidence of EEC in Europe[4] it must be considered that not all babies born in Germany with EEC could be included in the CURE-Net database, although great effort was undertaken from the CURE-Net participants and the self-help groups to motivate families to take part. From incidence data from Cervellione et al for the year 2010[4] we can conclude that only 50% of the German EEC babies in total, in detail 67% of the German CBE newborn babies were recruited for the CURE-Net evaluation in that specific year. Additionally and as the German health system is decentralized, only random parts of the cross-sectional EEC patients living in Germany took part in the study.

CONCLUSION

The large nationwide multicenter data collection of any associated anomalies within the EEC spectrum detected a

higher rate of urological anomalies within the spectrum and a higher rate of heart, abdomen, skeleton, and joint anomalies outside the spectrum. These might be either important in terms of predictable comorbidity for preparing the primary reconstruction in the newborn or infant period or later in the long-term follow-up. Their clinical relevance suggests considering them before initial operative treatment. As any associated anomalies were present in 48 up to 59% of affected EEC individuals possibly associated anomalies should be evaluated during routine check-up in all EEC patients.

Acknowledgments. The authors would like to thank all families and patients who participated in this project.

Literature

1. Nelson CP, Dunn RL, Wei JT. Contemporary epidemiology of bladder exstrophy in the United States. *J Urol*. 2005;173:1728–1731.
2. Reutter H, Boyadjiev SA, Gambhir L, et al. Phenotype severity in the bladder exstrophy-epispadias complex: analysis of genetic and nongenetic contributing factors in 441 families from North America and Europe. *J Pediatr*. 2011;159:825–831.
3. Jayachandran D, Bythell M, Platt MW, et al. Register based study of bladder exstrophy-epispadias complex: prevalence, associated anomalies, prenatal diagnosis and survival. *J Urol*. 2011;186:2056–2060.
4. Cervellione RM, Mantovani A, Gearhart J, et al. Prospective study on the incidence of bladder/cloacal exstrophy and epispadias in Europe. *J Pediatr Urol*. 2015;11:e1–e6.
5. Suson KD, Inouye B, Carl A, et al. Congenital renal anomalies in cloacal exstrophy: is there a difference? *J Pediatr Urol*. 2016;12:207.. e1-5.
6. Stec AA, Baradaran N, Gearhart JP. Congenital renal anomalies in patients with classic bladder exstrophy. *Urology*. 2012;79:207–209.
7. Gupta DK, Charles AR, Srinivas M. Exstrophy variants: should they be considered malformation complexes separate from classic exstrophy? *Eur J Pediatr Surg*. 2003;13:377–382.
8. Reutter H, Bökenkamp A, Ebert AK, et al. Possible association of Down syndrome and exstrophy-epispadias complex: report of two new cases and review of the literature. *Eur J Pediatr*. 2009;168:881–883.
9. Promm M, Gerling S, Ebert AK, et al. Congenital heart defects in patients with bladder exstrophy —a so far neglected association? *J Pediatr Urol* 2016;. S7-6 (PP).
10. Lowentritt BH, Van Zijl PS, Frimberger D, et al. Variants of the exstrophy complex: a single institution experience. *J Urol*. 2005;173:1732–1737.
11. Botto LD, Khoury MJ, Mastroiacovo P, et al. The spectrum of congenital anomalies of the VATER association: an international study. *Am J Med Genet*. 1997;71:8–15.
12. Gearhart JP. The bladder exstrophy-epispadias-cloacal exstrophy complex. In: Gearhart JP, Rink RC, Mouriquand PDE, eds. *Pediatric Urology*. Philadelphia: WB Saunders Co.; 2001:511.
13. Martínez-Frías ML, Bermejo E, Rodríguez-Pinilla E, et al. Exstrophy of the cloaca and exstrophy of the bladder: two different expressions of a primary developmental field defect. *Am J Med Genet*. 2001;99:261–269. Apr 1.
14. Winter RM, Baraitser M, Douglas JM. A computerised data base for the diagnosis of rare dysmorphic syndromes. *J Med Genet*. 1984;21:121–123.
15. Schwedler G, Lindinger A, Lange PE, et al. Frequency and spectrum of congenital heart defects among live births in Germany. A study of the competence network for congenital heart defects. *Clin Res Cardiol*.. 2011;100:1111–1117.
16. Adam M, Hudgins L. The importance of minor anomalies in the evaluation of the newborn. *Neo Rev*. 2003;4:e99–103.

EDITORIAL COMMENT

The authors present a large Multicenter German Study looking at the association between the exstrophy epispadias complex (EEC) and other congenital anomalies. The database was created from patient's entering the CURE-net system, which started in 2009. In the prospective group, the authors have identified 73 patients born between the years of 2009 and 2016. They also identified a larger group of 162 patients which they label as a cross-sectional group who were recruited from EEC born between 1948 and 2008. By far the most valuable of the groups is the prospective group which includes the 73 patients starting in 2009.

The authors' series does point out several intriguing and interesting associations some of which are different from previously published reviews of anomalies associated with the EEC. The first of these would be that exstrophy variants were found in 21% of the current review, which is significantly higher than previously reported. The authors found that associated anomalies outside the EEC were discovered, in 59% of their prospective group including renal anomalies in 18% and genital anomalies other than the epispadias component in 18%. They also pointed out that females in their study group were found to have Mullerian duct abnormalities to a far greater extent than had previously been reported with 65.7% experiencing Mullerian duct abnormalities such as uterine or vaginal duplication obstruction or absence.

Although the authors' data is compelling, it may not give the full picture due to a lack of mandatory reporting congenital anomalies through a centralized birth registry in German. The number of pregnancies in which the EEC was discovered and terminated before birth are not documented and no further valid data are available such as other anomalies which might have been present. Although, much of the data is intriguing and thought provoking, I am not entirely sure that it in any way changes our approach to the care of the infant born with EEC. Most of these patients are completely investigated, thus few, if any of the anomalies reported would be inadvertently overlooked.

Terry W. Hensle, MD., FACS, FAAP, Columbia University College of Physicians and Surgeons, New York City, NY

https://doi.org/10.1016/j.urology.2018.05.047
UROLOGY 123: 219, 2019.

AUTHOR REPLY

We greatly appreciate the Editorial Comment on our article "Association Between Exstrophy-Epispadias Complex And Congenital Anomalies: A German Multicenter Study." Here the question has been raised whether the observations of our study

might change the approach to the care of newborns with exstrophy-epispadias complex (EEC).

In our study, we compared 2 EEC cohorts. The prospective cohort comprised patients approximately 1 year old at the time of data acquisition and a cross-sectional cohort of older EEC patients. Patients in the prospective cohort were born between 2009 and 2016. Patients in the cross-sectional cohort were born between 1948 and 2008. We observed more exstrophy variants and co-occurring congenital heart defects in our prospective cohort compared to our cross-sectional cohort ($P < .0001$ and $P = .003$, respectively). Moreover, we observed more co-occurring congenital anomalies in our prospective cohort compared to our cross-sectional cohort, although this difference was not significant ($P = .16$).

While exstrophy variants constitute very rare orchids within the EEC spectrum, we believe that only the exact preoperative assessment of these exstrophy variants guarantees the best operative care. Furthermore, the correct assessment of the cardiovascular status prior to major reconstructive surgery will reduce the congenital heart defects associated perioperative risks. Hence, stage of the art treatment should encounter the exact assessment of the patients' phenotype, including all co-occurring congenital anomalies.

In this respect, we would like to quote the German poet and philosopher Johann Wolfgang von Goethe [1749-1832] who said "We only see what we know."

We deliberately advocate that if prenatal diagnosis raises the suspicion of an EEC phenotype, or when a newborn presents with anomalies of the EEC spectrum, the respective parents or newborns should be forwarded to a specialized pediatric urology department for further consultation and ultimate operative treatment.

Prior to an immediate postnatal transfer, we urge the primary physician to get in touch with a specialized pediatric urology department to receive consultation for the initial assessment. We urge these physicians to seek advice on the opportunities for initial conservative treatment regimens including the coverage of the bladder plate with a sterile gauze, allowing the newborn and the mother to bond instead of separating an otherwise healthy newborn from his mother.

Up to now, we are certain that even if Germany had a nationwide centralized birth registry, the primary physician who assesses the fetus prenatally or the newborn at birth could only then register the case with an anomaly of the EEC spectrum "if he knows what he sees."

We believe, that only the thorough assessment of a newborn with a complex urogenital anomaly in a specialized pediatric urology department will guarantee the best care, a matter of course, far from the current practice.

Anne-Karoline Ebert, MD, Nadine Zwink, PhD, Heiko Martin Reutter, PhD, MD, Department of Pediatric Urology, University Hospital for Urology and Pediatric Urology Ulm, Ulm, Germany; Department of Child and Adolescent Psychiatry, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany; Institute of Human Genetics, University of Bonn, Bonn, Germany; Department of Neonatology and Pediatric Intensive Care, Children's Hospital, University of Bonn, Bonn, Germany

https://doi.org/10.1016/j.urology.2018.05.048
UROLOGY 123: 219–220, 2019.