Syndromology of anorectal malformations revisited: from patterns of associated malformations to the recognition of syndromes

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Review article

***Background*: Although the frequency of associated malformation is high, the incidence of inheritable syndromes is widely underestimated in children with anorectal malformation (ARM).**

***Data resources*: OMIM database, patient records and charts of the Department of Pediatric Surgery, Johannes Gutenberg-University, Mainz, Germany.**

***Methods*: We analyzed all associations, sequences and syndromes listed in the OMIM database that can be accompanied by ARM. A large cohort of children born with ARM was then retrospectively investigated as to the type of ARM, presence of additional malformations and possible categorization as a syndrome, sequence or association. For this process a syndrome finder was developed and employed. This simplistic tool allows for a rapid first check of possible syndromes before a more complex analysis is started using the OMIM database and consulting specialists.**

***Results*: Among 317 children with ARM, associated malformations were present in 77.7% of 127 children with high ARM, in 68.7% of 32 with intermediate ARM, and in 25.3% of 158 with a low type ARM. Three or more organ systems were involved in 29.1% children with high type ARM and 25% with intermediate ARM and 8.2% with a low type ARM. An association of the vertebral anal tracheo-esophageal renal (VATER) and vertebral anal cardiac tracheo-esophageal renal limb (VACTERL) type was found in a total of 35 patients. Before analysis, 11 syndromes and 35 associations which were not clear previously in this patient cohort were described. In other 17 patients, 14 syndromes and 3 associations were identified.**

***Conclusions*: The high number of only retrospectively identified syndromes suggests that a routine search is necessary in every patient with ARM and additional malformations.**

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***Key words*: anorectal malformation;
associated malformation;
association;
syndrome;
VACTERL/VATER**

Introduction

Because of their embryopathology, anorectal malformations are frequently associated with other malformations. Migrational arrest of the mesoderm at the caudal stump and an abnormal resorption of the cloacal membrane are thought to induce anal atresia and other anorectal malformations. Newer embryological concepts based on comparative animal experiments question this conventional concept.[1] However, other organs that originate from mesodermal tissues are often subject to malformation in children with congenital anorectal abnormalities. Pediatricians and pediatric surgeons are familiar with these associated malformations which were first summarized under the acronym VATER (**V**ertebral **A**nal **T**racheo-**E**sophageal **R**enal) in 1972.[2] Later, the letters C (cardiac) and L (limb) were added and the term VACTERL was coined. Two or three of the respective malformations were taken as a requirement to fulfill the definition of a VATER or VACTERL association in different publications. Depending on the definition, the incidence of VATER/VACTERL associations is between 523/3 000 000 (VACTERL≥2)[3] and 286/10 000 000 live births (VACTERL≥3).[4] Most pediatric and surgical textbooks are limited to mentioning the associated malformations listed in this acronym but do not give any further information on associated malformations of anorectal malformation (ARM). VACTERL, however, is an association and not a syn-

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drome.[4] Although numerous genetic syndromes include anorectal malformations, this aspect remains largely unknown. Especially in multiple anomalies a syndromologic categorisation may be very difficult or even impossible since a considerable overlap between different syndromes exists and incomplete manifestations of syndromes are common. Therefore in clinical routine, most cases of multiple anomalies including anorectal malformation (ARM) will be named VACTERL. In the last 50 years more and more such patients have survived. A central question for patients and their parents is the risk for repetition in further children and inheritance to next generations of a malformation. This question cannot be answered correctly before ruling out all possible genetic syndromes that include an ARM. While the respective risks are very low in VACTERL associations,[5,6] they may reach up to 100% in certain syndromes. The challenge of a syndromologic categorisation can either be transferred to a specialized pediatrician or be made by a general pediatrician or pediatric surgeon using reference books (Leiber: the clinical syndromes, e. g.) or computer databases such as OMIM (Online Mendelian Inheritance in Man, Johns Hopkins University, Baltimore, USA: http://www3. ncbi. nlm. gov/omim/). This article incorporates an analysis of all data from this database on syndromes and associations that include anorectal malformations.

Methods

The data on type of ARM and associated malformation of 317 children treated at a single university hospital (Mainz, Germany) from 1968 to 2001 were computed into a Microsoft Access© database. The pattern of malformations was analysed with regard to the severity of ARM (high, intermediate or low type ARM according to the wingspread classification).

All available data from the OMIM database on syndromes and associations that include ARM not only sporadically but frequently were collected and summarized. The bulk of data was concentrated to a cluster sheet (syndrome finder) for a rapid orientation.

To test the efficacy of the scheme that was developed by this process, the data from the patient cohort were analysed according to the new method for rapid identification of frequent syndromes in ARM. All children with more than one malformation were first checked by the syndrome finder and then analysed by entering the malformation pattern into the OMIM database online. If no syndrome could be identified and 3 or more malformations, which belong to the spectrum of a VACTERL association, were present, the malformation pattern was classified as VATER or VACTE-RL.

Results

Among the 317 children with ARM (155 boys and 162 girls), 127 had a high ARM, 32 had intermediate and 158 had a low type ARM. Associated malformations were present in 77.7% children with high type ARM, in 68.7% with intermediate type ARM, and in 25.3% with low type ARM. Multiple malformations with 3 or more organ systems involved were seen in 29.1% children with high type ARM, and in 25% with intermediate ARM and in 8.2% with low type ARM. The most frequently affected organ systems were the urogenital system and the skeletal system. Only half that frequent were malformations of the gastrointestinal tract, the cardiovascular system and the central nervous system (Table 1).

Table 1. Organ systems involved and malformations found with types of ARM

Organ system	Malformation	ARM type			Total	
		high	intermed	low		
Kidney, ureters, bladder	Kidney dys/agenesis	30	4	8	42	138
	Horse shoe kidney	5	-	1	6	
	Pelvic duplication	10	1	3	14	
	Rotational anomaly	7	-	-	7	
	VUR	17	4	5	26	
	hydronephrosis	14	1	3	18	
	Sinus/cloaca	14	-	-	14	
	Neurogenic bladder	9	1	1	11	
Male + female genitalia	Hypospadia	6	1	3	10	60
	Scrotal dysplasia	5	-	-	5	
	Cryptorchidism	8	-	2	10	
	Maldescensus testis	16	3	1	20	
	Female internal genitalia	11	1	3	15	
Spine and ribs	Cervical spine	4	1	-	5	105
	Thoracic spine	6	3	2	11	
	Lumbar spine	15	2	3	20	
	Sacrum	35	4	6	45	
	Scoliosis	5	2	2	9	
	Ribs	9	3	3	15	
Gastrointestinal	Esophageal atresia	17	3	2	22	50
	Duodenal atresia/sten	4	1	1	6	
	Meckel diverticulum	7	1	-	8	
	Hirschsprung's	1	-	1	2	
	IND	3	2	3	8	
	Mal/nonrotation	-	1	1	2	
	Duplication	-	-	1	1	
	Biliary atresia	-	-	1	1	
Nervous system sensory organs	CNS	5	1	2	8	74
	Microcephaly	2	-	5	7	
	Retardation	12	1	8	21	
	MMC	5	-	1	6	
	Dysrhaphy	4	1	2	7	
	Eye	2	4	4	10	
	Ear	6	3	6	15	
Total		294	49	84		427

intermed: intermediate.

Urogenital tract malformations associated with ARM

The most frequent malformations were those of kidney organ development, such as dys- or agenesis of one or both kidneys, horse shoe kidney and duplication of the pelvic system or rotational anomalies of the kidney. Urine transport anomalies such as vesicoureteral reflux or hydronephrosis were frequent as well. Urogenital sinus or cloaca were present in 14 children with high type ARM, a neurogenic bladder was found in 11 mainly with high type ARM (Table 1). Cryptorchidism and maldescensus testis as well as penoscrotal malformations were associated especially with high type ARM. In girls, malformations of the inner genitalia were seen more frequent with high type ARM.

Skeletomuscular system malformations associated with ARM

In numerous children with high type ARM, anomalies especially of the lumbar and sacral spine were found. The cervical and thoracic spine as well as the ribs were less frequently affected but most often in high type ARM.

Gastrointestinal tract malformations associated with ARM

Again, malformations (such as atresia of the esophagus and duodenum or Meckel diverticula) of this organ system were prevalent in high type ARM. Innervation disorders (Hirschsprung's disease and intestinal neuronal dysplasia), however, were frequent in low type ARM.

Malformations of the nervous system associated with ARM

In contrast to most other organs systems, the central and peripheral nervous system and the sensory organs were subject to structural and functional disorders in all types of ARM independent of the severity of ARM.

Non syndromic multiple malformation patterns

An association of the VATER and VACTERL type was found in 35 patients of the current study. Among the 127 patients with high type ARM, a VATER association was found in 17, a VACTERL in 7, and a VACTERL + H in 1. Within the 32 patients with intermediate type ARM, there was a VATER in 1, a VACTERL in 2, and a VACTERL + H in 1. With low type ARM (148 patients), 5 VATER and 1 VACTERL association were seen. Table 2 shows detailed information on the number and type of organ systems involved in the respective patients and the frequency of occurrence among ARM types.

Table 2. Pattern of malformations found in children with different severity of VATER/VACTERL associations and different severity of ARM

Organ system	High	Intermediate	Low	Total
V	18	3	4	25
A	25	4	6	35
C	8	2	6	16
T	12	3	2	17
E	12	3	2	17
R	18	3	2	23
L	6	2	-	8
H	1	1	-	2
Association				
VATER 3	10	1	3	14
VATER 4	5	-	2	7
VATER 5	2	-	-	2
VACTERL 3	-	-	1	1
VACTERL 4	3	-	-	3
VACTERL 5	1	1	-	2
VACTERL 6	3	1	-	4
VACTERL 7	-	-	-	-
VACTERL + H	1	1	-	2
Frequency	25/127(19.7%)	4/32(12.5%)	6/148(4.0%)	

Malformation syndromes

The malformation syndromes, associations and sequences listed below were observed among the 317 patients with ARM, a considerable number, however, were identified only after systematic effort was made to identify the syndromes by a OMIM-assisted search. The list is made in the order of the frequency of occurrence in the patient cohort observed.

Down-syndrome (*OMIM #190685*) [7-10]

Five children presented with Down's-syndrome (trisomy 21), 2 with high type ARM, 2 with intermediate ARM, and 1 with low type ARM. Two had additional intestinal malformations (1 Hirschsprung's,[11] 1 intestinal neuronal dysplasia).

OEIS-complex (*OMIM 258040*) [12]

The "omphalocele-exstrophy-imperforate anus-spinal defects-complex" was found in 3 children who presented with omphalocele, vesicointestinal fissure, high type anal atresia (partial or total colonic aplasia) and a meningocele or spina bifida occulta with tethered cord.

Currarino-syndrome (*OMIM #176450*) [13]

Three girls showed sacral dys- or agenesis, a presacral tumor (1 meningocele, 1 dermoid, 1 teratoma) and an ARM (2 high type ARM, 1 anal stenosis).

Cat eye-syndrome (*OMIM #115470*) [14]

Two girls with low type ARM, numeric aberration of

chromosome 22 (1 tetrasomy 22, 1 trisomy 22), preauricular fistula ($n=1$) or auricular appendix ($n=1$), and cardial malformation (1 ASD, 1 ASD + pulmonary stenosis). Bilaterally dysplastic kidney was found in 1 child, extrahepatic biliary atresia with hypoplastic gallbladder in 1 and Hirschsprung's disease in 1.

Radial aplasia x-linked syndrome (OMIM 312190) [15]

In 2 boys with high type ARM, esophageal atresia type IIIb and radial aplasia bilaterally, one had hypospadia, testicular aplasia and horse shoe kidney and the other hydronephrosis. One child with a dysplastic 4th cervical spine, 13 pairs of ribs were present; however hydrocephalus was not found which may belong to the syndrome.

Johanson-Blizzard-syndrome (OMIM* 243800) [16]

One boy with high type ARM, pancreatic insufficiency, aplastic gallbladder, deafness, and psychomotoric retardation. Hypoplasia of the alae nasi and hypothyroidism were not described in this patient.

Casamassima-Morton-Nance-syndrome (OMIM 271520) [17]

One boy with high type ARM, multiple dysplastic ribs, split thoracic vertebral bodies (Th 3-5), dysplasia of the lumbar vertebral bodies (L 2-5), sacral dysplasia, dysplastic right kidney, complex cardiac malformation, encephalocele and agenesis of the coecum and appendix.

ROCA Wiedemann-syndrome (OMIM 604690) [18]

One girl with high type ARM, psychomotoric developmental delay, ptosis of the eye lids, epikanthus, deep insertion of the ears, hexadactyly of the extremities, microcephaly, epilepsy, hypotonia, and dysplastic right double kidney.

Split notochord-syndrome [19]

One boy with high type ARM with dorsal ectopic rectal fistula, lumbar MMC, malformation of the lumbar and sacral spine, hydrocephalus with Arnold-Chiari II -malformation, hypoplastic right tibia and clubfoot.

Association of esophageal atresia anal atresia and Mayer-v. Rokitansky-Küster-Hauser syndrome

One girl with high type ARM, esophageal atresia (type VI a according to Kluth's classification) with an esophageal lung, duodenal atresia, aplastic left kidney, dextrocardia and aplasia of the uterus and vagina. This case was recently published,[20] only one similar case was reported previously.[21]

Ivemark-syndrome (OMIM 208530)

Two boys with high type ARM. A) complex cardiac malformation with pulmonary vein malinsertion, ASD, VSD, ductus botalli, coronary anomaly, dysplastic right double kidney, VUR °III-IV, and cerebral coordination disorder.* B) situs ambiguus, aplastic right kidney, and sacral dysplasia.

Cornelia de Lange syndrome (OMIM #122470)*

One boy with high type ARM, microcephaly, aplastic left kidney, typical facies, aplasia of the right thumb and hypoplasia of the first metacarpal, 14 rib pairs, dysplastic right ear, and retardation.

CHARGE-syndrome (OMIM #214800)*

One boy with high type ARM, choanal stenosis bilaterally, microphthalmia, ear malformation, deafness, split vertebral body Th 3, sacral hypoplasia, bilateral cervical ribs, spina bifida occulta, and malformations of both hands and feet.

Furthermore, a Zachary-Morgan-syndrome was identified in one child with congenital short colon and high type ARM. Fanconi-syndrome (OMIM#227650) with multiple malformations,[22,23] a Klippel-Feil-malformation, and a Potter-sequence were found in one child with ARM.

Prior to the current analysis, 11 syndromes and 35 associations were described in this patient cohort. In other 17 cases, 14 syndromes and 3 associations which were not clear previously, were now identified. Fourteen of these could be classified reliably while 3 can only be assigned with a certain probability. These cases are marked by an asterisk. Altogether 63 of the 317 children with anorectal malformation were characterized by syndromes or associations with a majority of them in the group of high type ARM. Therefore, an incidence of 20% of syndromes or associations in the whole group or of 33% among those with high type ARM was confirmed by the present data (Table 3).

In summary, 427 additional malformations were found in 162 of the 317 children with ARM. The remaining 155 children with ARM had no additional malformation. Therefore the total incidence of additional malformations in ARM is more than 50%. Among those with additional malformation 66 had one additional malformation and 96 had several additional malformations. In the 96 children with at least 3 malformations, including ARM, 26 were found a syndrome, 35 an association, and the remaining 35 no classification (Table 4).

Table 3. Left column: associations, sequences and syndromes identified in the patient cohort prior to the present analysis. Right column: newly identified syndromes and associations in the same cohort by applying the syndrome finder and OMIM-database search

Syndrome/association, previosly detected	*n*	Syndrome/association, newly identified	*n*
VATER/VACTERL-association	35	VACTERL + H	2
Down-syndrome	5	OEIS-syndrome	3
Ivemark-syndrome	1	Ivemark-syndrome	1
Currarino-syndrome	1	Currarino-syndrome	2
Zachary-Morgan-syndrome	1	Cat-eye-syndrome	2
Fanconi-syndrome	1	Radial aplasia x-linked	2
Klippel-Feil-syndrome	1	ROCA-Wiedemann-syndrome	1
Potter-sequence	1	Split-notochord-syndrome	1
		Casamassima-Morton-Nance-s.	1
		Cornelia de Lange-syndrome	1
		CHARGE-syndrome	1
Number of syndromes, sequences or associations	46	Number of newly identified syndroms or associations	17

Table 4. Syndrome-finder for rapid first orientation in syndromal categorization of multiple malformations associated with ARM. All syndromes that regularly incorporate imperforate anus are listed, other about 50 syndromes that only occasionally are associated by ARM are not listed

Syndrome	OMIM	skull	CNS	mental	facial	cardial	vertebral	arm	hand	leg	foot	lung	trachea	esophagus	duodenum	Small bowel	colon	renal	genital	sacral	stature
ABAR	600123	■			■	■		■	■												
Currarino	*142994						■													■	
Down	#190685			■	■	■			■		■				■		■				■
CEPI	260450					■						■				■					
TRAL	274265																	■			
OEIS	258040						■												■	■	
Joh.-Blizzard	*243800	■	■		■											■			■		■
PIV	174100						■		■												
Opitz G	*145410			■	■	■							■	■					■		
Pall.-Hall	#146510		■		■				■			■	■					■	■		
BGS	218600	■		■	■	■	■	■	■									■	■		
FG	*305450	■	■	■	■	■															■
Rieger	#180500	■			■													■			■
TBS	#107480			■	■	■		■	■									■			■
Amelia x	301090	■			■			■	■	■	■	■						■	■		
UMS	#181450							■	■				■			■			■		■
VATER	192350					■	■	■	■	■	■		■	■				■		■	
VACTERL+H	276950		■			■	■	■	■	■	■		■	■				■		■	
VACTERL+H X	*314390		■		■	■	■	■	■	■	■	■	■	■				■	■	■	
CES	#115470				■	■	■	■	■		■	■				■		■	■		
AA H PS inv	602553																		■		
ROCA	604690			■	■	■															■
CMN	271520				■	■	■											■	■		

Abbreviations used in table 4:

ABAR: Atrioventricular septal defect-blepharophimosis-anal and radial defects
Currarino: Currarino-triad: sacral agenesis-presacral mass-anorectal malformation
CEPI: Combined exocrine pancreatic insufficiency
TRAL: Thymic-renal-anal-lung dysplasia
OEIS: Omphalocele-extrophy-imperforate anus-spinal defect
Joh. -Blizzard: Johanson-blizzard-syndrome: nasal alar hypoplasia-hypothyroidism-pancreatic achylia-congenital deafness
PIV: Polydactyly-imperforate anus-vertebral anomalies
Opitz G: Hypertelorism-esophageal abnormality-hypospadia
Pall. -Hall: Pallister-hall-syndrome: hypothalamic hamartoblastoma-hypopituitarism-imperforate anus-postaxial polydactyly-syndrome
BGS: Baller-gerold-syndrome: craniosynostosis-radial aplasia-syndrome
FG: FG-syndrome: mental retardation-imperforate anus-congenital hypotonia-partialagenesis of corpus callosum
TBS: Townes-brock-syndrome: renal-ear-anal-radial-syndrome
Amelia x: Amelia x-linked: amelia-facial cleft-absence ears/nose-atresia ani
UMS: Ulnar-mammary-syndrome
VACTERL + H: VACTERL-hydrocephalus
VACTERL + HX: VACTERL-hydrocephalus, x-linked
CES: Cat-eye-syndrome: chromosome 22 partial tetrasomy-iris coloboma-anal atresia-preauricular pits/tags-heart-renal
AA H PS inv: Anal atresia-hypospadia-penoscrotal inversion
ROCA: ROCA-Wiedemann-syndrome: growth/developmental retardation-ocular ptosis-cardiac defect-anal atresia
CMN: Casamassima-Morton-Nance-syndrome: spondylocostal dysostosis-anal atresia-urogenital anomalies

Discussion

In the literature, a considerable variance of the incidence of VATER/VACTERL associations in groups of patients with ARM can be found. The range of the incidence is from 39/208 (18.8%) or 52/140 (37.4%)[24,25] to 116/264 (44%),[26] in contrast to the low incidence of 35/317 (11%) in the present study. These differences between studies have different reasons: 1. the proportion of high vs low type ARM since additional malformations are much more frequent in high ARM; 2. the proportion of boys vs girls since additional malformations are more frequent in boys; 3. the definition of VATER/VACTERL which is used differently;[27] 4. the different quality of analysing patients with multiple anomalies which are sometimes uncritically summarized as VATER/VACTERL although distinct syndromes are present.[28] The high number of syndromes that were only identified retrospectively in the current report highlights this aspect. Therefore, a clear analysis of the associated malformations with regard to a possible symdromologic classification is proposed in all children with ARM and multiple malformations. Although this process may be complicated and time consuming,[29] it presents the only reliable way to rule out genetically inheritable syndromes, which is a prerequisite for genetic counselling of parents and affected children. The syndrome finder as described in this paper gives the reader the opportunity to perform the first step of such a syndrome search process by simple measures without the requirement of a computer or connection to a database. However two important aspects have to be considered with this simplified method. First, not a definite diagnosis rather a suspicion can be made, which needs further evaluation of the respective literature and details as given in the OMIM database and/or consultation from a specialist. Second, the syndrome finder lists only the 23 most important and frequent syndromes and associations while other 50 syndromes can be found in the OMIM database that only sporadically coincide with ARM. Therefore, neither exclusion nor definite confirmation of a certain syndrome is possible with this simplistic tool. But, raising a suspicion may be the first step for a more straightforward analysis and a definitive diagnosis. As evident from the high incidence of associations and syndromes accompanying ARM in this report, a high level of suspicion is justified especially in children with high type ARM and several other malformations.

The second focus of this report is on the incidence and type of associated malformations with ARM. Some earlier reports only give data on specific organ systems such as the urogenital tract,[30-32] the cardiovascular system,[33] or the spine.[34,35] Other papers display the full spectrum of anomalies in larger patient cohorts,[7,36-38] but without providing details on these malformations and without making a special analysis of possible syndromes behind the associated multiple malformations. The current data give some additional information for the identification of malformation patterns that are typical with ARM and associated syndromes.

Identifying or excluding a genetically inheritable syndrome in a patient with ARM is a duty of both pediatricians and pediatric surgeons involved.

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