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Vascular Biology and Vascular Medicine

Assessment of Congenital Vascular and Organ Anomalies in Subjects With Thalidomide Embryopathy Using Non-Contrast Magnetic Resonance Angiography

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Background: To determine the type and frequency of vascular and organ malformations in adults with thalidomide embryopathy (TE) using non-contrast magnetic resonance angiography (MRA) and to assess the effect of the observed malformations on renal function.

Methods and Results: The institutional ethics committee approved this prospective study and written informed consent was given by all 78 subjects (50 females) with TE (mean age: 55±1.1 years), who were examined by non-contrast MRA at 3T. ECG-triggered balanced turbo field echo images of the chest, abdomen and pelvis were obtained in coronal and sagittal orientations. Two observers assessed the frequency of vascular and organ malformations. Serum creatinine and estimated glomerular filtration rate (eGFR) were obtained to assess renal function. In 58 subjects, 99 vascular anomalies were observed, including 68 arterial (69%) and 31 venous anomalies (31%); 15 patients had 16 abdominal organ malformations including 12 kidney anomalies and 4 cases of gallbladder agenesis. Most vascular anomalies affected the renal vessels (n=66, 67%) or supraaortic arteries (n=28, 28%). Serum creatinine and eGFR revealed normal renal function in all subjects.

Conclusions: Vascular and organ anomalies occurred in a high number of subjects with TE without evidence of renal dysfunction. Information about the presence of malformations may be important for future surgical interventions in subjects with TE.

Key Words: Non-contrast magnetic resonance imaging; Thalidomide; Vascular and organ abnormalities

Thalidomide is an immunomodulatory drug that led to one of the most dramatic congenital disasters in medical history. Available without prescription, thalidomide was advertised as a sedative drug to treat anxiety, nausea and morning sickness.[1] Maternal intake of this drug between 1958 and 1963 resulted in 8,000–12,000 infants with thalidomide embryopathy (TE), mainly in Europe and Japan.[2] Dysmelia is a characteristic feature of TE, which includes malformations of the upper limb and ranges from deformation of the thumb and fingers to absence of the entire upper limb. In Germany, around 2,300 of 5,000 infants with TE are still alive and now in their 50 s.[3] Despite the well-known teratogenic effects, thalidomide is currently still prescribed to treat various diseases because of its immunomodulatory and anti-inflammatory properties. These diseases include multiple myeloma and erythema nodosum leprosum, which is an inflammatory complication of leprosy. Recently, new cases of TE were registered in Brazil, particularly in areas with endemic leprosy and where the dispensing of thalidomide is difficult to control.[4] Therefore, TE is not only a medical care issue for aging subjects in the Northern Hemisphere but also a present health threat for young families in the Southern Hemisphere.

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A recent clinical study revealed more cardiovascular events in adults with TE compared with the normal population and those authors postulated a possible vascular impairment related to TE.[5] The frequency and type of vascular and organ malformations was assessed in a pilot study by Tajima et al, who reported anomalies of the vascular system in 6 of 22 subjects (27%) with TE.[6] However, their study was limited by the relative small sample size, precluding a reliable estimation of anomaly frequencies,

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and by the use of a suboptimal imaging technique (unenhanced whole-body computed tomography) for evaluation of small arteries and veins.

Magnetic resonance angiography (MRA) using time-of-flight and phase-contrast techniques is a well-established method for depicting the arterial and venous vasculature without the need for intravenous contrast media, which can be problematic in TE subjects with dysmelia.[7] The additional advantages of balanced field turbo echo MRA are high spatial resolution and large scan volume, which enables imaging of the entire thorax and abdomen without patient or coil reallocation during the scan.[8]

The purpose of this study was to determine the type and frequency of vascular and organ malformations in adults with TE using non-contrast MRA and to assess the effect of the observed malformations on renal function.

Methods

Subjects

The institutional review board approved this prospective study and all subjects provided written informed consent. The 78 subjects, who were born between January 1958 and August 1963, included 50 females and 28 males with a mean age of 55±1.1 years who were examined between February 2016 and October 2017. All subjects had anomalies of the upper extremities and were recognized by the German Contergan Foundation as having TE. Information about the presence of diabetes type II and arterial hypertension was available in 73 (94%) and 71 (91%) of the subjects, respectively; 14 subjects had diabetes type II (19%) and 28 (39%) suffered from arterial hypertension. Subjects were asymptomatic for thoracic or abdominal vessel or organ malformations. Serum creatinine and estimated glomerular filtration rate (eGFR) data were available for 71 subjects (91%). Serum creatinine was defined as normal with <1.5 mg/dL for men and <1.4 mg/dL for women.[9] eGFR was defined as normal with >90 mL/min/1.73 m^2.[9] Morning spot urine sample was obtained in 39 subjects (50%) to analyze proteinuria. The urine albumin-to-creatinine ratio was categorized as normo- (<30 mg/g), micro- (30 to 300 mg/g) or macro-albuminuria (>300 mg/g).[9]

Classification of Upper Limb Dysmelia and Eye, Ear or Facial Anomalies

Subjects with TE were classified into 3 groups based on the extent of upper limb dysmelia according to the cephalocaudal sequence of malformation:[10] 23 subjects (29%) had dysmelia of the hand, ranging from minimal change with hypotrophic or absent thenar muscles to an absent thumb or absence of several fingers; 30 subjects (38%) had anomalies restricted to the forearm, varying from absence of the radius in the presence of the ulnar to total absence of the forearm with a normal proximal upper limb; 25 subjects (32%) had dysmelia of the upper arm with a dysplastic humerus and glenoid resulting in phocomelia with residual fingers. Information about eye, ear and face anomalies was retrieved from medical records; 7 subjects suffered from eye muscle paralysis; 12 subjects had auditory organ damage, including narrow internal auditory meatus (2 uni- and 3 bilateral), anotia (4), aplasia of the internal auditory meatus (3), aplasia of the vestibule (2). Of the 12 subjects with anomalies of the auditory organ, 6 (50%) had hearing loss. A total of 3 subjects had facial deformities: 1 subject had paralysis of the 7th cranial nerve; 1 subject had combined eye muscle paralysis and narrow internal auditory meatus with hearing loss; 1 subject had facial deformities and anotia, resulting in 21 subjects with TE and eye, ear or facial damage.

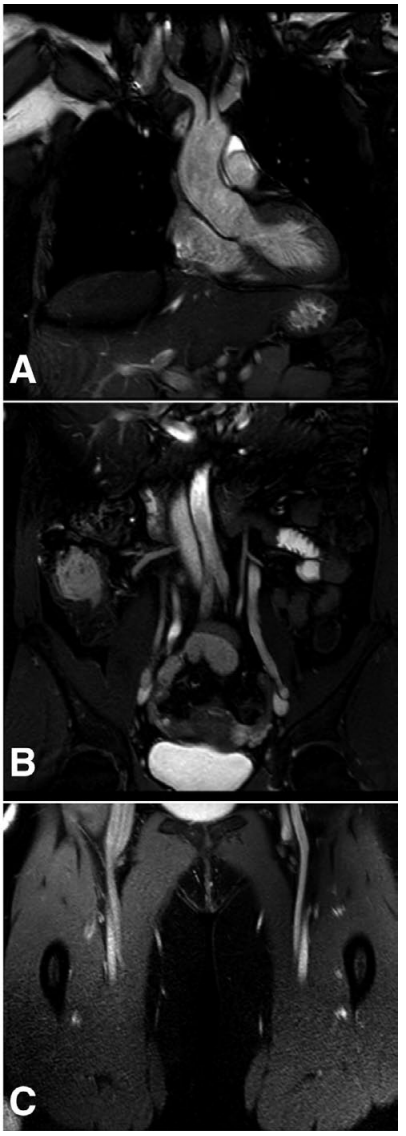

Figure 1. Non-contrast coronal MRA of thoracic (**A**), abdominal (**B**) and pelvic (**C**) vessels and organs in a subject with thalidomide embryopathy.

Non-Contrast MRA

Non-contrast MRA was performed using a 3T MR system equipped with a 16-channel coil (3.0 T Achieva with Sense XL torso coil, Philips Medical Systems, Best, The Netherlands). The coil size was 60×55.8×7.4 cm and covered the chest, abdomen and pelvis; 2 torso coils were used in larger subjects. Scout images were obtained in the axial, coronal and sagittal orientations. ECG-gated non-contrast 2D balanced field turbo echo imaging with sensitivity encoding (SENSE) images were acquired in the sagittal and coronal orientations (**Figure 1**). Breath-hold images were obtained at end-diastole to minimize motion artifacts.

Table 1. (A) Frequencies of Vascular and Organ Anomalies in 78 Subjects With TE Including Information About the Presence of Multiple Anomalies in a Given Subject, (B) Frequency and Location of Arterial and Venous Anomalies (n=99) in Subjects With TE

A. Frequency of anomaly	Vascular	Organ		Vascular or organ[a]
		Renal	Gallbladder	
No anomaly	20 (26)	66 (85)	74 (95)	16 (21)
1 anomaly	28 (36)	11 (14)	3 (4)	28 (36)
2 anomalies	22 (28)	1 (1)	1 (1)	22 (28)
3 anomalies	6 (8)	0	0	7 (9)
4 anomalies	1 (1)	0	0	4 (5)
5 anomalies	1 (1)	0	0	0
6 anomalies	0	0	0	1 (1)
Sum		78 (100)		

B. Vascular anomaly	Renal	Supraaortic	Other	Sum
Arterial	38 (38)	28 (28)	2 (2)	68 (69)
Venous	28 (28)	0	3 (3)	31 (31)
Sum	66 (67)	28 (28)	5 (5)	99 (100)

Data are number (n) and percentage (%). [a]Sum of subjects with combinations of vascular and organ anomalies. A subject with 3 anomalies could either have 1 vascular and 2 organ anomalies or 2 vascular anomalies and 1 organ anomaly. The subject with 6 anomalies had 5 vascular and 1 organ anomalies. TE, thalidomide embryopathy.

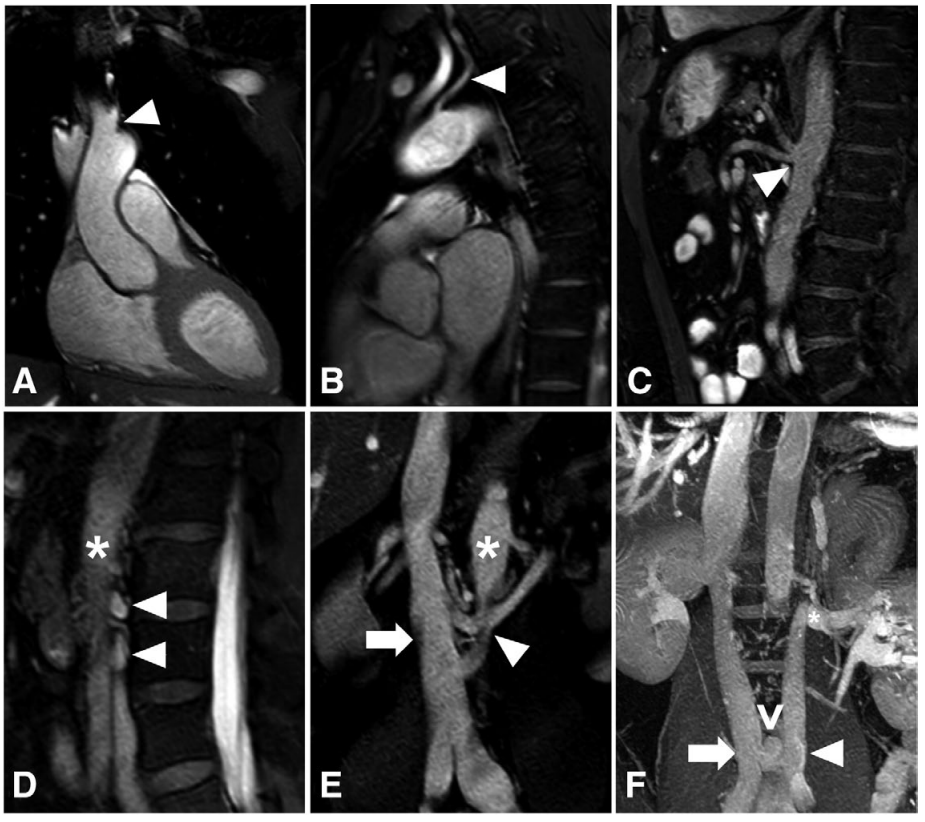

Figure 2. Arterial (**Upper**) and venous (**Lower**) anomalies in subjects with thalidomide embryopathy. (**A**) Coronal image of a bovine arch, (**B**) sagittal image of a left vertebral artery originating from aortic arch, (**C**) sagittal image of a coeliac-mesenteric trunk, (**D**) sagittal image of 2 retroaortic left renal veins (arrowheads), which travel between the spine and the abdominal aorta, (**E**) coronal image of 2 retroaortic veins (arrowheads), which originate from a single vessel and drain into the inferior vena cava (IVC, arrow). The bifurcation is located dorsal of the abdominal aorta (*). (**F**) Volume-rendered image of a duplicated left IVC (arrowhead), which originated from the left renal vein (*). The left IVC has no cranial run off but is connected via a transverse interiliac vein (open arrowhead) to the right IVC (arrow) at the lumbar level.

Table 2. Types of Arterial Anomalies in Subjects With Inferior Vena Cava and Normal Values From the Literature

Arterial anomalies	Normal value	Thalidomide (n=78, 100%)	Dysmelia restricted to			Eye, ear or facial damage (n=21, 27%)
			Hand (n=23, 29%)	Forearm (n=30, 38%)	Upper arm (n=25, 32%)	
Bovine arch	8–27.4[11,32]	17 (22)	3 (13)	3 (10)	11 (44)**	3 (14)
Arteria lusoria	1–1.2[11,32]	2 (3)	1 (4)	1 (3)	0	1 (5)
Left vertebral artery from aortic arch	4.1–6.6[11,32]	9 (12)*	4 (17)**	3 (10)	2 (8)	4 (19)**
Coeliomesenteric trunk	<1[33]	2 (3)	0	1 (3)	1 (4)	1 (5)
Doubled renal arteries	23[31]	29 (37)*	9 (39)	9 (30)	11 (44)	7 (33)
Tripled renal arteries	4[31]	5 (6)	3 (13)**	1 (3)	1 (4)	1 (5)
Renal artery from iliac artery	0.03–0.05[31,32]	4 (5)	1 (4)	3 (10)	0	2 (10)
Sum	NA	68	21	21	26	19

Data are number (n) and percentage (%), whereas normal values from the literature are given in percentage (%) only. *Indicates divergence from reported values in the literature. **Indicates accumulation of anomalies in subgroups. NA, not available.

Table 3. Types of Venous Anomalies in Subjects With Thalidomide Embryopathy and Normal Values From the Literature

Venous anomalies	Normal value	Thalidomide (n=78, 100%)	Dysmelia restricted to			Eye, ear or facial damage (n=21, 27%)
			Hand (n=23, 29%)	Forearm (n=30, 38%)	Upper arm (n=25, 32%)	
Retroaortic left renal vein	0.8–3.6[16,17]	12 (15)*	3 (13)	5 (17)	4 (16)	4 (19)
Doubled renal veins	15–30[31]	11 (14)	5 (22)	4 (13)	2 (8)	0
Tripled renal veins	NA	1 (2)	0	1 (3)	0	0
Renal vein draining into common iliac vein	0.03–0.05[34,35]	4 (5)	1 (4)	3 (10)	0	1 (5)
Duplicated IVC	0.2–3[18]	2 (3)	2 (9)**	0	0	1 (5)
Compression of right common iliac vein	NA	1 (2)	1 (4)	0	0	0
Sum	NA	31	12	13	6	6

Data are number (n) and percentage (%), whereas normal values from the literature are given in percentage (%) only. *Indicates divergence from reported values in the literature. **Indicates accumulation of anomalies in subgroups. NA, not available.

No subject was excluded because of MRA contraindication or claustrophobia. All studies were diagnostic with good to excellent image quality. Image parameters were: TR/TE: 2.6/1.03 ms; flip angle: 60°; SENSE factor 2; field of view: feet-heel 280 mm, right-left: 381 mm, anterior-posterior: 169 mm; matrix: 192×192; acquired voxel size: 1.2×1.2×4 mm; reconstructed voxel size: 0.6×0.6×4 mm; slice thickness: 4 mm; number of slices: 56 with 8 slices per breath hold, gap: −1 mm. Scan time was 35–45 min, depending on body size and heart rate.

Vascular and Organ Evaluation Criteria

Radiologists with 8 and 4 years of experience, respectively, and blinded to the patients' information evaluated the MRA images in consensus according to the following criteria. A normal branching pattern of the aortic arch was defined in the presence of a brachiocephalic trunk, a left common carotid artery and a left subclavian artery. A bovine arch was defined if the left common artery arose from the brachiocephalic trunk. A separate offspring of the left vertebral artery as the last vessel from the aortic arch was defined as anomalous.[11] A common offspring of both the coeliac and superior mesenteric arteries was defined as a coeliac-mesenteric trunk.[12] Normal renal vascular anatomy was defined in the presence of 1 renal artery and 1 renal vein on each side arising from or draining into the abdominal aorta or the inferior vena cava (IVC), respectively. Kidneys were considered normal if they were paired and slightly obliquely positioned.[13]

Results

Vascular and Organ Anomalies

A total of 115 anomalies were found in 62 of the 78 subjects (79%), including 99 vascular anomalies in 58 subjects (74%) and 16 organ anomalies in 15 subjects (19%); 28 subjects (36%) had a single vascular or a single organ anomaly, 22 subjects (28%) had 2 anomalies, 7 subjects (9%) had 3 anomalies, 4 subjects (5%) had 4 anomalies and 1 subject (1%) had 6 anomalies (**Table 1A**). Of the 99 vascular anomalies, 68 (69%) were related to the arteries, and 31 were venous anomalies (31%) (**Table 1B**). The renal vessels were most frequently involved in 66 of the 99 vascular anomalies (67%), followed by the supraaortic arteries with 28 anomalies (28%) (**Table 1B**).

Arterial Vascular Anomalies

A total of 17 subjects had a bovine arch, 2 had an arteria lusoria and 9 had a left vertebral artery originated from the aortic arch (**Figure 2**). A coelio-mesenteric trunk was found in 2 subjects. Doubled and tripled renal arteries were found in 29 and 5 subjects, respectively (**Table 2**). The renal artery originated from the common iliac artery in all 4 subjects with a pelvic kidney. Comparison of the observed frequencies with reported frequencies from the literature revealed that subjects with TE more often had a left vertebral artery originating from the aortic arch, doubled renal arteries and a renal artery from an iliac artery (**Table 2**). Examples of arterial and venous anomalies are shown in **Figure 2**.

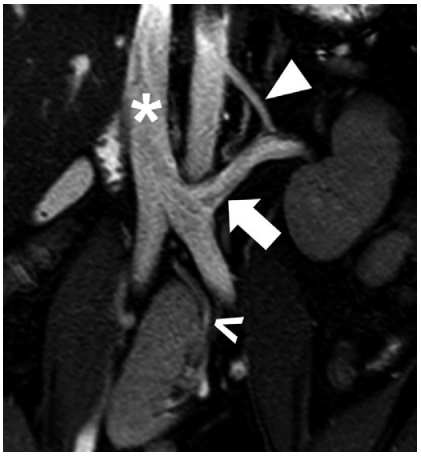

Figure 3. Coronal image of a subject with thalidomide embryopathy and a right pelvic kidney and a normal located left kidney. The renal artery of the right pelvic kidney (open arrowhead) originates from the right iliac artery. The left renal artery (arrowhead) originates from the aorta. A large left renal vein (arrow) drains into the inferior vena cava (*). The right renal vein is not depicted on this image.

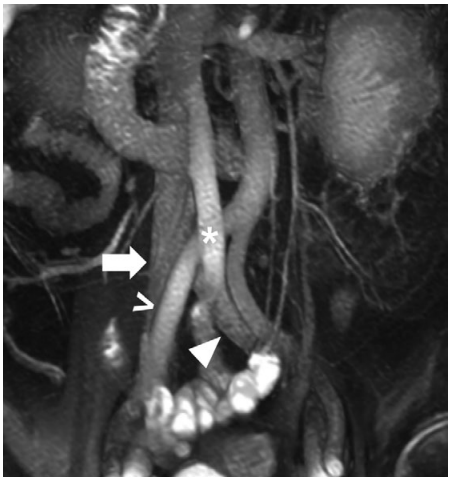

Figure 4. Volume-rendered image of another case of duplicated inferior vena cava (IVC). The left-sided IVC (*) arises from the common left iliac vein (arrowhead) and is located anterior of the right common iliac artery (open arrowhead). The duplicated left IVC drains into the right IVC (arrow) just below the left renal vein.

Table 4. Types of Organ Anomalies in Subjects With Thalidomide Embryopathy and Normal Values From the Literature

Organ anomalies	Normal value	Thalidomide (n=78, 100%)	Dysmelia restricted to			Eye, ear or facial damage (n=21, 27%)
			Hand (n=23, 29%)	Forearm (n=30, 38%)	Upper arm (n=25, 32%)	
Single kidney	0.04[36]	4 (5)*	2 (9)	1 (3)	1 (4)	1 (5)
Pelvic kidney	0.03–0.05[31,32]	4 (5)*	1 (4)	3 (10)**	0	2 (10)**
Malrotated kidney	NA	3 (4)	2 (9)	0	1 (4)	1 (5)
Duplex kidney	0.7[34]	1 (1)	1 (4)	0	0	1 (5)
Gallbladder agenesis	0.01–0.75[27]	4 (5)*	0	3 (10)**	1 (4)	2 (10)**
Sum	NA	16	6	7	3	7

Data are number (n) and percentage (%), whereas normal values from the literature are given in percentage (%) only. *Indicates divergence from reported values in the literature. **Indicates accumulation of anomalies in subgroups. NA, not available.

Venous Vascular Anomalies

A retroaortic left renal vein was the most frequent venous anomaly, which occurred 15% more often in subjects with TE compared with the normal value of 0.8–3.6% (**Table 3**). A total of 11 subjects had doubled renal veins and 1 subject had tripled renal veins. In 3 of the 4 subjects with a pelvic kidney the renal vein drained into the common iliac vein. In the 4th subject, the right renal vein drained into the IVC while the renal vein of the normally located left kidney drained into the common iliac vein (**Figure 3**); 2 subjects had a duplicated IVC, shown in **Figure 2F** and **Figure 4**.

Organ Anomalies

A total of 15 patients had 16 abdominal organ malformations, including 12 kidney anomalies and 4 cases of gallbladder agenesis. Kidney anomalies included 4 single kidneys (1 right, 3 left), 4 pelvic kidneys (3 right, 1 left), 3 malrotated kidneys and 1 duplex left-sided kidney with a normal right kidney (**Table 4**). Of the 4 subjects had a gallbladder agenesis, 1 also had a pelvic kidney. Single, duplex and pelvic kidneys and gallbladder agenesis occurred more often in subjects with TE compared with frequencies in the literature (**Table 4**).

Association Between Vascular and Organ Anomalies and Extent of Dysmelia

No specific pattern was found for arterial, venous or organ anomalies with a clear association between the extent of dysmelia and frequency of organ anomalies. However, a bovine arch occurred 44% most often in subjects with dysmelia of the upper arm, while a left vertebral artery originating from the aortic arch (17%) and tripled renal arteries (13%) occurred more often in subjects with dysmelia of the hand (**Table 2**). A duplicated IVC occurred only in subjects with dysmelia of the hand (**Table 3**). Pelvic kidneys and gallbladder agenesis occurred more often in subjects with dysmelia of the forearm (**Table 4**).

Association Between Vascular and Organ Anomalies and Eye, Ear or Facial Anomalies

A left vertebral artery originating from the aortic arch, pelvic kidneys and gallbladder agenesis seemed to occur more in subjects with eye, ear or facial anomalies (**Tables 2**,**4**). Other than these anomalies, there was no

clear association between vascular and organ anomalies and eye, ear or facial anomalies.

Renal Function in Subjects With TE

All subjects had normal creatinine and normal eGFR data. Mean serum creatinine and eGFR were in the normal range at 0.77±0.18 mg/dL and 93±11 mL/min, respectively. All subjects with a retroaortic left renal vein had similar serum creatinine and eGFR levels of 0.83±0.2 mg/dL and 92±13 mL/min, respectively, compared with 50 subjects without a retroaortic renal vein or renal malformation who had 0.77±0.18 mg/dL and 94±11 mL/min, respectively. Serum creatinine and eGFR data were available in 11 of the 12 subjects with kidney malformations, and were normal at 0.78±0.11 mg/dL and with 94±8 mL/min, respectively. Of 39 subjects with available urine albumin data, 34 (87%) had normoalbuminuria of 5.9±2.6 mg/g (range: 2–12 mg/g) and 5 had microalbuminuria of 74±59 mg/g (range: 31–177 mg/g). None of the subjects had macroalbuminuria. Of the 5 subjects with microalbuminuria 2 had diabetes type II and arterial hypertension, 2 had arterial hypertension and 1 subject had neither diabetes nor arterial hypertension, but a malrotated kidney.

Discussion

We successfully determined the frequency of vascular and organ malformations in asymptomatic adults with TE using non-contrast MRA. We also analyzed the effect of the observed malformations on renal function and compared the observed frequencies with reported values from the literature. The main findings of our study were as follows. (1) Vascular anomalies were found in 74% of the study subjects with TE. (2) Two-thirds of the vascular anomalies were related to the arteries and one-third to the veins. Most of the vascular anomalies were within reported frequencies; however, supernumerary renal arteries, left vertebral artery originating from aortic arch and a retroaortic left renal vein occurred more often in subjects with TE than previously reported. (3) Subjects with TE also had abdominal organ anomalies, most often involving the renal system with single, pelvic, duplicated and malrotated kidneys. (4) We found no evidence that the observed vascular or organ malformations had affected renal function in the current study's long-term survivors with TE. However, knowledge about possible malformations is important for subjects with TE in case of future abdominal surgical or vascular treatment.

Effect of Thalidomide on the Vascular and Renal Systems

Our findings suggested that thalidomide had mainly affected renal vessels, because we found the largest variations from reported normal values in the number of renal arteries and in the retroaortic course of the left renal vein. Because we did not have any information about the time point and frequency of maternal thalidomide intake during pregnancy, we cannot draw any direct conclusions about the sensitive period of this drug. However, embryological studies may give some clues. During weeks 6 and 9 of human embryological development the kidneys ascend from an initial sacral level to a final position at the upper lumbar level. This ascent of the kidneys is paralleled by development of transitory arterial vessels, which originate from the aorta. The final renal arteries arise from the lumbar part of the aorta, while the transitory vessels usually disappear.[14] Hypotheses suggests that renal malposition with pelvic kidneys might be related to persistent transitory vessels, which physically block the ascent of the kidneys from the pelvis to its normal lumbar position.[14,15] Our observation that all 4 renal arteries and 3 renal veins in the 4 subjects with pelvic kidneys originated from the common iliac artery or iliac veins fits with this hypothesis.

Embryological studies also indicate that improper completion of the complex embryological development of the retroperitoneal venous system can result in malformations of the renal veins and the IVC.[16] A retroaortic left renal vein was the most frequent venous malformation in subjects with TE and showed the highest difference to reported values.[16,17] One potential explanation could be that thalidomide prevented normal regression of the circumaortic venous plexus, resulting in displacement of the left renal vein. We found 2 cases of IVC duplication, which is within the range of reported frequencies.[18] However, the anatomic course of the observed IVC duplications did not match commonly known IVC duplications.[19] According to a proposed classification the duplicated left-sided IVC drains into the left renal vein, which drains into the right sided IVC.[19] Both of the present cases of IVC duplication had distinctly different drainage. In 1 subject, the left renal vein drained into the duplicated left IVC, which was transversely connected to the right IVC at the lower lumbar level. In the second subject, the left IVC arose from the left common iliac vein, located anterior of the right common iliac artery, and drained into the right IVC just below the left renal vein. These 2 cases suggest that thalidomide resulted in unusual, currently unknown IVC duplications.

Effect of Thalidomide on Abdominal Organs

We only observed malformations of the abdominal organs, mainly the kidneys, which including single, duplicated, malrotated and malpositioned kidneys. Furthermore, 4 subjects had gallbladder agenesis. These findings in adult subjects with TE are less severe than the early postmortem examinations and clinical studies of children with TE from the 1960s, which included abdominal malformations such as duodenal atresia and anteriorly displaced anal orifices requiring surgical intervention.[20–22]

Possible Molecular Pathway of Thalidomide Teratogenesis

The teratogenic effects of thalidomide has been have been recently discovered.[23,24] Eichner et al showed that both the antiangiogenic and teratogenic effects of thalidomide were exerted via the protein cereblon. In a zebrafish model thalidomide binds to and inhibits cereblon, which is essential for a complex developmental cascade resulting in limb outgrowth and expression of the fibroblast growth factor 8.[24] Eichner et al demonstrated that thalidomide inhibited vasculogenesis, which was preceded by reduced expression of fibroblast growth factor 8 and cell death in the limb buds, resulting in decreased size of the head and eyes. Furthermore, it was shown that loss of fibroblast growth factor 8 function led to development abnormalities of the brain and kidneys.[25] Even though the described pathways may not be entirely reproducible in humans, it might explain the frequent vascular, kidney, auditory and facial malformations found in the current study.

Clinical Consequences of the Observed Anomalies

A previous study suggested that a retroaortic course of the left renal vein can lead to increased pressure in the renal

vein because of the compression of this vessel between the aorta and the spine.[26] Furthermore, it was postulated that this venous congestion resulted in proteinuria.[26] However, all our subjects with a retroaortic left vein had normal serum creatinine levels and none had microalbuminuria. In 4 of the 5 subjects with microalbuminuria, there was no evidence of either diabetes type II or arterial hypertension, which would be the most likely causes for microalbuminuria in these subjects.[27] Knowledge of the anatomy of the abdominal organs and vessels is important for any invasive or minimally invasive surgical procedure in this region.[28,29] A study of the surgical repair of abdominal aneurysms reported a high incidental injury rate of retroaortic left renal veins during surgery, which led to nephrectomy and death in 2 cases each.[29] Thus, the course of the renal vein and presence of a doubled IVC is important information with regard to any surgical intervention of the abdominal aorta, because incidental injury of these vessels is a severe surgical complication. A case report highlighted the importance of exact preoperative knowledge of the patient's anatomy;[30] in this case the patient presented with symptoms mimicking gallbladder pathology, which resulted in an attempted, but unsuccessful laparoscopic cholecystectomy. Postoperative MR imaging confirmed gallbladder agenesis, which in retrospect made the surgical intervention unnecessary. This unwanted outcome could have been avoided by timely use of imaging. Therefore, we recommend preoperative imaging of the abdominal organs and vessels in any subject with TE, preferably non-contrast MRA to accurately depict any anomalies and to plan the operative strategy.

Study Limitations

First, the number of subjects was relative small, but this was the first systematic study of vascular and organ malformations in subjects with TE. Second, we did not have a control group to analyze the normal frequencies of the observed malformations. To overcome this limitation, we compared the observed frequencies with reported normal values in the literature. This approach is limited, because the reported normal values were obtained within the past 4 decades using different techniques such as postmortem autopsies, venography and computed tomography. These variable reference methods possibly resulted in inconsistent findings. Furthermore, no information was available in the cited literature about the combined occurrence of vascular and organ anomalies or of vascular anomalies in different anatomic locations, such as supraaortic and renal vessel anomalies.[11,16–18,30–37] Based on the current findings we calculated a sample size of 400 subjects with TE and 400 controls to show significant differences in frequent malformations such as a retroaortic left renal vein. Third, our data most likely represented a positive selection of subjects with less severe TE because we only studied subjects with TE and dysmelia restricted to the upper limbs. It is possible that subjects with malformations of the lower extremities have more profound vascular and organ anomalies. Furthermore, our study population was biased because we studied subjects with TE who had survived >50 years, representing a positive selection of our population.

Conclusion

Non-contrast MRA revealed a high number of vascular and abdominal organ anomalies in subjects with TE. All subjects with vessel or kidney anomalies had normal renal function, suggesting a benign nature of these malformations in the current study's long-term survivors with TE. Nevertheless, the current findings are essential for any physician who is involved in the patient care of subjects with TE. We recommend preoperative imaging of the abdominal vessels and organs in subjects with TE scheduled for surgery, preferably by non-contrast MRA to depict the anatomy and to plan the operative strategy.

Disclosures

U.W. is an employee of Philips Healthcare, Hamburg, Germany. The other authors report no conflicts.

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