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# MR of the Caudal Regression Syndrome: Embryologic Implications

R. A. J. Nievelstein, J. Valk, L. M. E. Smit, and C. Vermeij-Keers

**PURPOSE:** To evaluate the spectrum of developmental anomalies observed in patients with the caudal regression syndrome and relate them to the pathogenesis of this syndrome. **METHODS:** Nineteen children with caudal regression were investigated with MR. **RESULTS:** The level of vertebral agenesis varied from T-11 to S-5. In 9 of the 19 children the characteristic high-ending wedge-shaped cord terminus was observed. A separation of the anterior and posterior spinal roots of the cauda equina was observed in 9 patients. Four patients had a tethered spinal cord, in 1 in combination with a wedge-shaped cord terminus. **CONCLUSIONS:** The pathogenesis of the caudal regression syndrome can be divided into two kinds: there is usually a disturbance of the primary neurulation process; in other cases there is a derailment of the process of degeneration and differentiation of an initially normally developed primary and secondary neural tube. MR aids understanding of the morphology and pathogenesis of congenital malformations involved (including the associated anomalies of the genitourinary and gastrointestinal systems), but other studies are still necessary to determine the exact mechanism of this syndrome.

**Index terms:** Spinal cord, congenital anomalies; Spine, abnormalities and anomalies; Spine, magnetic resonance; Spine, vertebrae; Pediatric neuroradiology

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Caudal regression is a relatively rare congenital anomaly characterized by caudal vertebral agenesis or dysgenesis (including hemisacral anomalies), most often in combination with spinal cord malformations (1-3). When associated with several other congenital anomalies, especially of the genitourinary and gastrointestinal systems, it is usually called the syndrome of caudal regression (1, 2, 4-6). The incidence of this syndrome is approximately 0.01 to 0.05 per 1000 births, and in 16% of these children the mothers were diabetic during pregnancy (6-8).

Patients with the caudal regression syndrome are usually first investigated for neurologic, urologic, and orthopedic complaints (1, 2, 6, 7). The neurologic manifestations include motor and sen-

sory deficit that usually correspond to the level of vertebral agenesis, although in some patients the sensory functions persist below this level (6, 9). The urologic symptoms are mainly associated with neurologic bladder impairment. The clinical manifestations of the caudal regression syndrome follow.

## Neurologic anomalies:

Segmental deficit, corresponding to the level of vertebral agenesis, predominantly motor impairment with relative sparing of the sensory function

Neurogenic bladder

Bowel incontinence or obstipation

Absent or pathologic deep tendon and skin reflexes

Dimples

## Orthopedic anomalies:

Caudal vertebral agenesis (usually sacroccygeal)

Dysraphic or dysplastic vertebral defects

Hip dislocation or dysplasia

Frog-leg position (and popliteal webbing)

Club feet

Narrow pelvic region

Sirenomelia

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**Genitourinary anomalies:**

- Hydronephrosis
- Renal dysplasia or agenesis
- Dysplasia or agenesis of other parts of the genitourinary system
- Renal ectopia

**Gastrointestinal anomalies:**

- Imperforate anus or anorectal atresia
- Fistulas
- Esophageal or duodenal atresia

Traditionally, plain-film radiography and myelography supplemented by computed tomography have been the studies of choice (10). Recently, magnetic resonance (MR) has made it possible to demonstrate not only the spinal cord and spine malformations, but also most of the associated anomalies observed, especially of the genitourinary and gastrointestinal systems. The most characteristic MR finding in the caudal regression syndrome is caudal vertebral agenesis together with a high-ending wedge-shaped cord terminus (7).

To understand the combination of congenital malformations observed in the caudal regression syndrome, knowledge of the normal embryonic development of the caudal region is essential. In the literature, two major points of discussion still exist concerning the embryogenesis of this syndrome: the level of closure of the caudal neuropore (10–12), and the developmental processes involved (ie, the process of primary or secondary neurulation) (1, 2, 5, 7, 13–16). However, recent embryologic observations by Nivelstein et al concerning the normal embryonic development of the caudal neural tube in human embryos have elucidated these items (17). The purpose of the paper presented here is to describe the MR characteristics of the caudal regression syndrome in relation to these embryologic observations.

**Patients and Methods**

MR studies (0.6-T Teslacon II, General Electric, Milwaukee, Wis) were evaluated in 19 patients with caudal regression syndrome, 9 girls and 10 boys, with an average age of 6.2 years (range, 4 days to 21.2 years). They initially presented mainly with neurologic problems (11 patients), orthopedic problems (6 patients), genitourinary malformations (3 patients), and/or gastrointestinal malformations (10 patients) (Table). Most patients had more than one symptom. All 10 patients with gastrointestinal malforma-

tions had anorectal atresia. In 2 of these patients MR was performed preoperatively and in 8 postoperatively. Four of the 19 patients had diabetic mothers (patients 1, 2, 9, and 14; Table). Although sometimes indicated as caudal regression, patients with genitourinary and gastrointestinal malformations without spinal anomalies were excluded.

Sagittal spin-echo T1-weighted images with 300–565/20–22/6 (repetition time/echo time/excitations), axial spin-echo T1-weighted images with 260–760/20–22/4–6, and coronal spin-echo T1-weighted images with 260–615/20–22/4–6 of the lumbosacral spine and pelvic region were performed on each patient. In 10 of the 19 patients sagittal gradient-echo T2-weighted images with 165–170/32/8, 10° to 12° flip angle and/or axial gradient-echo T2-weighted images with 270–285/32/6, 10° to 12° flip angle, of the lumbosacral spine were also obtained. A surface receiving coil was used, and the section thickness was kept as thin as possible (usually 5 mm) with a small intersection gap (1.25 mm).

Evaluation of each imaging study included detection of the level of vertebral agenesis, dysraphic and/or dysplastic anomalies of the last vertebrae, level and shape of the spinal cord terminus, abnormal course of the spinal roots of the cauda equina, and any other spinal cord abnormality. The vertebral anomalies as determined with MR were compared with the observations on plain-film radiography of the lumbosacral spine when available. The associated anomalies were evaluated only when visualized adequately.

**Results***MR of the Spine and Spinal Cord*

The MR findings of each patient are summarized in the Table. MR effectively depicted the level of vertebral agenesis in all and the dysraphic and/or dysplastic vertebral anomalies in most patients. The last vertebra was T-10 in 1 patient (Fig 1), L-4 to L-5 in 4 patients, and S-1 to S-4 in 14 patients (Table). One of these 14 patients had a hemisacrum (patient 15) (Fig 2). In 18 of 19 patients the last one or two vertebrae were dysraphic and/or dysplastic. Partial fusion of the iliac bones was observed in 3 of the 5 patients with a vertebral agenesis above S-1.

The most characteristic shape of the spinal cord terminus in this syndrome is the wedge-shaped cord terminus, that is, the dorsal aspect of the cord extending more caudally than the ventral portion, which was observed in 9 of the 19 patients (Table and Fig 3). Of the remaining 10 patients 4 had more bulbous or blunted cord termini (Fig 4), and 3 had tethered spinal cords. In 2 patients the conus were normal. Evaluation of the cord terminus was not possible in patient 1 because of inadequate visualization (Fig 1). A



Patients with a caudal regression syndrome as determined by MR

Patient	Sex/Age	Presenting Symptoms	Last Vertebra	Conus		Separation of Spinal Roots?	Tethered Lesion?	Level of Neurologic Deficit
				Level	Shape			
1	F/10 d	Frog legs	T-10	>T-10	...	...	...	±T-10
2	M/4 d	Thoracic dimple Lower extremity weakness Club foot	L-5	T-11	WS	Yes	No	L-4-L-5
3	M/9.3 y	Hip dysplasia Anal atresia	L-5	T-11	WS	Yes	No	...
4	F/2 mo	Lower extremity weakness Club foot Hip dislocation	L-5	T-12	WS	Yes	No	L4
5	M/1.4 y	Neurogenic bladder Lower extremity weakness	S-1	T-12	WS	Yes	No	L-5-S-1
6	M/7 mo	Neurogenic bladder Lower extremity weakness Club foot	S-1	T-12	WS	Yes	No	L-5
7	F/3.5 mo	Anal atresia	S-1	T-12	B	Yes	No	...
8	M/4 y	Hypospadia Anal atresia	S-2	T-12	WS	Yes	No	S-2
9	F/13 y	Neurogenic bladder	S-2	L-1	B	No	No	S-2
10	M/11.3 y	Neurogenic bladder	S-3	T-12-L-1	WS	Yes	No	S-2
11	M/21.2 y	Anal atresia	S-3	L-1	B	No	No	...
12	F/16.8 y	Neurogenic bladder Anal atresia	S-3	T-12	WS	Yes	No	S-2
13	F/4.1 y	Esophageal atresia Lower extremity weakness Club foot	S-4	T-12-L-1	B	No	No	S-1
14	F/1.2 y	Neurogenic bladder Club foot	L-5	T-12-L-1	WS	No	Fibrolipoma of filum	L-4-L-5
15	F/1.6 y	Bladder extrophia Anal atresia Omphalocele	S-3 Hemisacrum	S-1-S-2	T	No	Fibrolipoma conus	S-1
16	M/5.5 y	Anal atresia Esophageal atresia Renal agenesis	S-3	L-3	S	No	Fibrolipoma of filum	S-2
17	M/21.2 y	Neurogenic bladder Anal atresia	S-4	L-5	S	No	Fibrolipoma of filum	S-2
18	F/3.3 y	Anal atresia	S-4	L-1	N	No	No	S-2
19	M/3.7 y	Anal atresia Esophageal atresia	S-4	L-1-L-2	N	No	No	N

Note.—WS indicates wedge-shaped; B, blunted; T, tethered; and S, stretched.

wedge-shaped cord terminus in combination with a fibrolipoma of the filum terminale was observed in patient 14 (Fig 5).

The level of the spinal cord terminus was situated above L-1 in 12 patients (most often opposite T-12), and opposite L-1 in 4 (Table). In the 3 patients with tethered spinal cords, the cord termini were situated between L-3 and S-2 (Fig 2).

The last intact spinal roots corresponded in most patients to the level of vertebral agenesis. An abnormal course of the spinal roots of the cauda equina, that is, a separation of the anterior and posterior spinal roots, was observed in 9 of the 19 patients (Table and Figs 6A and 6B). In

one of these 9 patients part of the lumbar roots was also absent or extremely hypoplastic unilaterally, despite a present fifth lumbar root and normal lumbar vertebrae (patient 5) (Fig 6C).

Associated spinal cord abnormalities included a syringohydromyelia in three patients (Fig 2).

#### MR of the Associated Anomalies

In most patients the genitourinary system was adequately visualized. The malformations observed included hydronephrosis (five patients), renal ectopia (three), renal dysplasia or agenesis (two), and distended bladders (seven) (Fig 7).



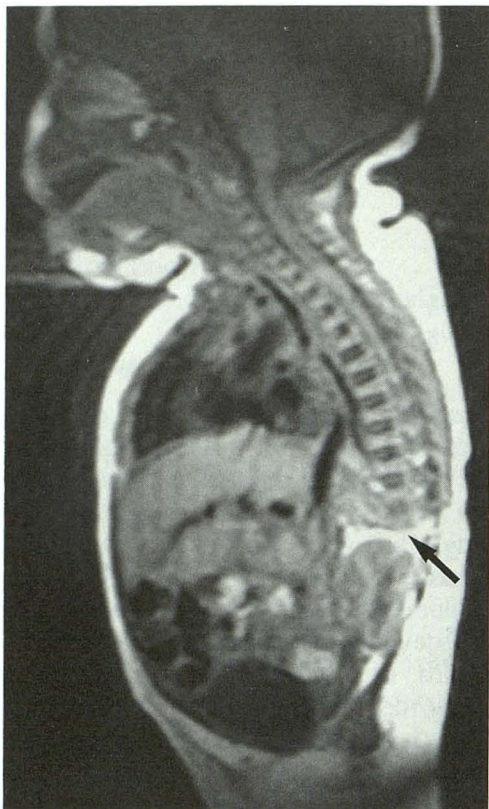


Fig. 1. Sagittal spin-echo T1-weighted image in a girl, 10 days of age, with a high level of vertebral agenesis (patient 1). The vertebral column terminates at T-10 (arrow).

In the patients with anorectal malformations special attention was paid to the pelvic region. In the 2 patients analyzed preoperatively the level of anal atresia was determined with MR; it seemed to be a high level in both (Fig 8A). The pelvic musculature was adequately visualized in 8 of the 10 patients. In 3 patients (1 preoperatively analyzed and 2 postoperatively) the puborectal muscles and external anal sphincters were extremely hypoplastic (Fig 8B). In the 8 postoperatively analyzed patients the positioning of the neorectums in the muscle complexes could be evaluated; in 3 patients it was inadequate. Severe fecal impaction or distended rectosigmoid was observed in 4 patients.

### Neurologic Symptoms

The level of neurologic deficit corresponded in general to the level of vertebral agenesis depicted with MR (Table). In most patients the sensory function was impaired to a lesser extent than the motor function. However, in young children determination of the sensory deficit is difficult and therefore probably not always adequate. That is

why the level of neurologic deficit in the Table is indicated only by the level of motor impairment.

### Discussion

In the evaluation of the caudal regression syndrome, MR enables adequate diagnosis not only of the congenital anomalies of the spinal cord and spine, but also of most of the associated anomalies in the pelvic region. This makes MR superior to imaging modalities such as plain-film radiography and computed tomography (myelography). Although plain spine radiography and computed tomography more readily determine osseous anomalies, MR effectively depicted the levels of vertebral agenesis in all and the dysraphic and dysplastic anomalies in most patients presented in this study. The characteristic wedge-shaped cord terminus was observed in 9 of the 19 patients in the present study (7). This wedge-shaped appearance may explain the frequent clinical observation that the sensory deficit occurs at a lower level than the motor deficit (6, 9). Seven of the 9 patients with wedge-shaped cord termini showed this relative sensory sparing, although it was also observed in 4 of the 8 patients

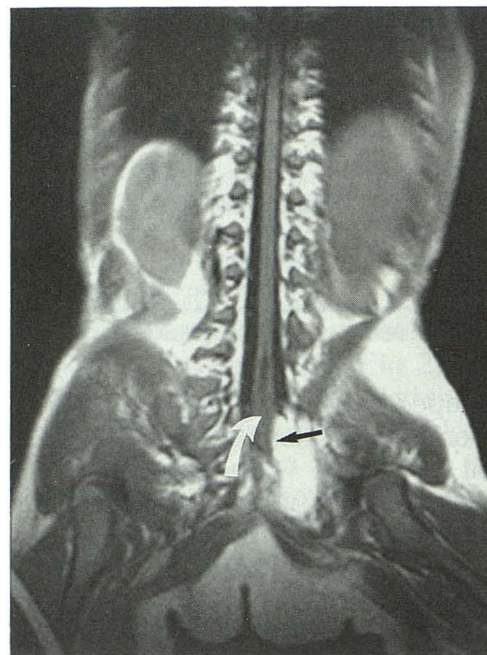


Fig. 2. Coronal spin-echo T1-weighted image in a girl, 1.6 years of age, with a hemisacral agenesis and a tethered spinal cord (patient 15). On the left side the sacrum terminates at S-1, on the right side at S-3. The spinal cord terminus is tethered in a sacral fibrolipoma (black arrow). A syrinx can be identified at the caudal end of the spinal cord (curved white arrow).



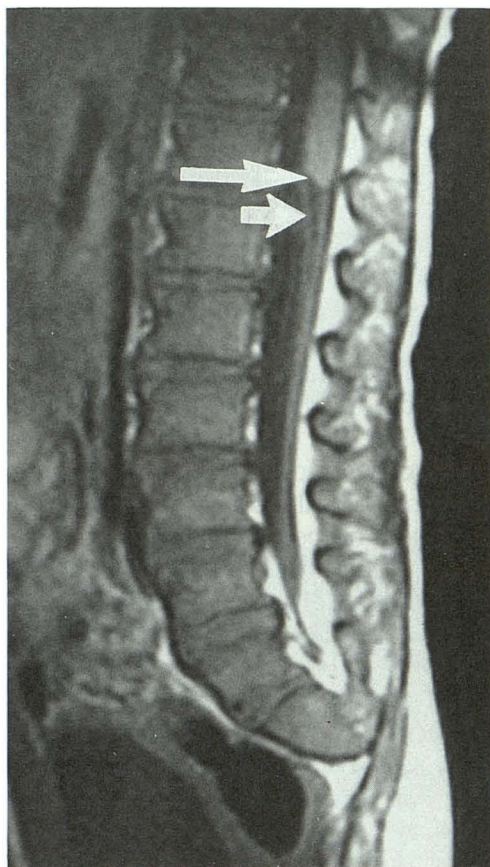


Fig. 3. Sagittal spin-echo T1-weighted image in a boy, 4 years of age (patient 8). The vertebral column terminates at S-2, and the characteristic wedge-shaped cord terminus can be identified opposite T-12 (*long arrow*). The anterior and posterior spinal roots are partially separated (*short arrow*).

with blunted conus or tethered spinal cords. It is noteworthy that in one patient not included in the present study, the wedge-shaped cord terminus was observed in combination with a normal spine.

Patients with caudal regression may have progression of their neurologic symptoms, as was observed in patient 16 in the present study (14). These progressive neurologic symptoms occur mostly in congenital malformations such as tethered spinal cords, which are often surgically correctable (7, 14, 18). Detection of these malformations with MR, preferably before (further) neurologic deterioration has taken place, makes early surgical correction possible. In the present study, four patients with tethered spinal cords were identified with MR, in one in combination with a wedge-shaped cord terminus. Only one of them (patient 16) underwent surgical correction, resulting in a slight neurologic improvement.

A hitherto undescribed MR finding, observed in nine patients, is the accentuated separation of anterior and posterior spinal roots at the level of the cauda equina. This MR finding was also observed in some patients with neurologic symptoms without spinal cord and spine malformations. In the literature, absence of spinal roots not corresponding to the level of vertebral agenesis, and aberrant courses of spinal roots have been described (9). In patient 5, MR suggested a unilateral absence of a few lumbar roots despite a present fifth lumbar root. However, the neurologic deficit did not correspond to this apparent absence, and, therefore, it may be secondary to the level of MR section.

An additional advantage of MR over other imaging modalities is the accurate visualization of associated congenital malformations, especially of the genitourinary and gastrointestinal systems. With respect to genitourinary malformations, MR seems to be most useful in visualizing renal agenesis, dysplasia, and/or ectopia. In cases with anorectal malformations, MR allows determination of the level of anorectal atresia and

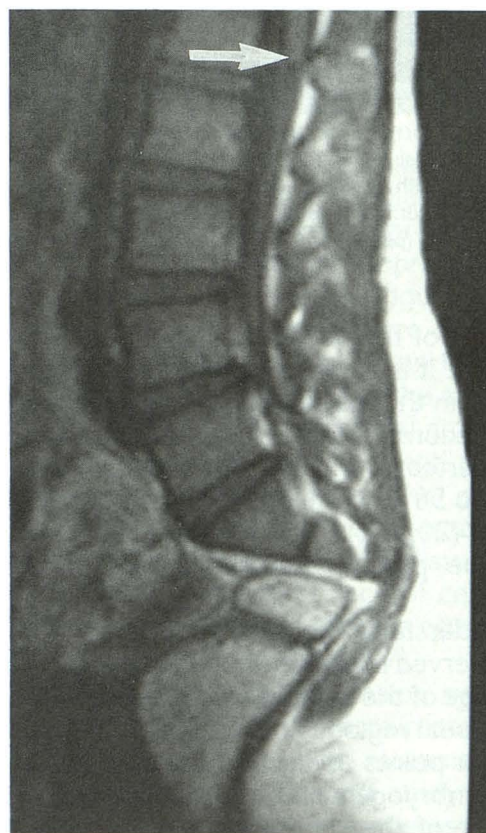


Fig. 4. Sagittal spin-echo T1-weighted image in a girl, 13 years of age, with a blunted spinal cord terminus opposite L-1 (*arrow*) (patient 9). The vertebral column terminates at S-2.



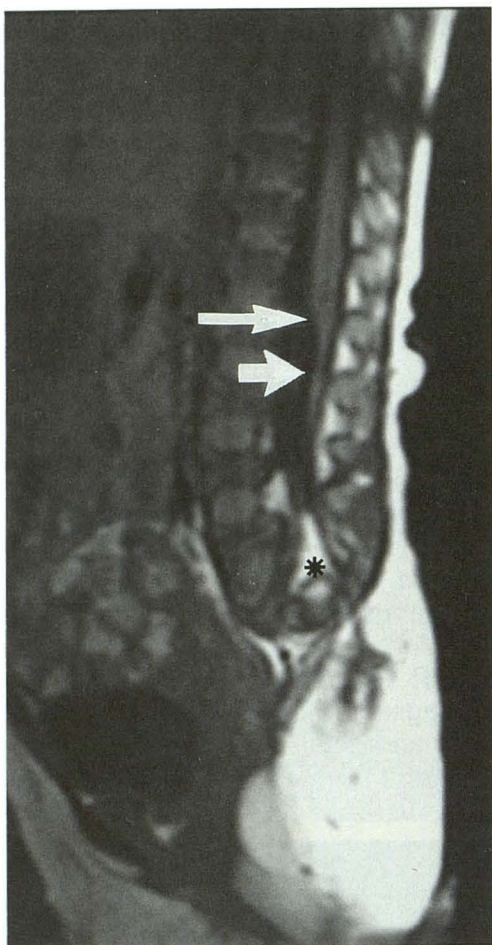


Fig. 5. Sagittal spin-echo T1-weighted image in a girl, 1.2 years of age, with a wedge-shaped cord terminus (*long arrow*) and fatty filum terminale (*short arrow*) tethered in a sacral fibrolipoma (*asterisk*) (patient 14). The vertebral column terminates at L-5.

evaluation of the pelvic musculature in anatomic detail (19). It is striking that anorectal atresia was observed in the majority of patients in the present study. According to Smith et al and Karrer et al, caudal vertebral and spinal cord anomalies occur in 40% to 50% of children with anorectal malformations (20, 21). Therefore, special attention should be paid to caudal regression in these children.

To understand the combination of malformations observed in the caudal regression syndrome, knowledge of the normal embryonic development of the caudal region is necessary. In the literature, two major points of discussion still exist concerning the embryogenesis of this syndrome: the level of closure of the caudal neuropore (10–12), and the developmental processes involved (ie, the process of primary or secondary neurulation) (1, 2, 5, 7, 13–16). It is important to know the exact

level of closure of the caudal neuropore, because caudal neuropore closure marks the end of the process of primary neurulation and, therefore, determines which part of the neural tube is formed during the primary and secondary neurulation processes, respectively (22). The opinions expressed in the literature concerning this final level vary from the second lumbar segment to the midsacral segments (10–12, 22–24). Recently, Nievelstein et al demonstrated that caudal neuropore closure in human embryos is situated at the level of the somites 32 to 34, which correspond to the third to fifth sacral vertebrae (17). Based on this observation, they conclude that the process of primary neurulation leads to the formation of all spinal cord segments, all spinal ganglia, and corresponding somites (future vertebrae). During the secondary neurulation process, a small additional part of the neural tube and the corresponding somites (future os coccygeus) are formed, both derived from the primitive streak. Out of that part of the neural tube only the filum terminale and ventriculus terminalis will develop by a process of degeneration (physiologic cell death, or, apoptosis) and differentiation of the secondary neurectodermal cells. This process of degeneration and differentiation takes place after 7 weeks of development and continues far into the second trimester of pregnancy (17). Simultaneously with this process, the mesenchymal vertebrae (ie, the somites during the neurulation process) differentiate by chondrofication and ossification, which continue after birth until adolescence (25).

The above-described embryologic processes, the processes of primary neurulation, secondary neurulation, and degeneration and differentiation, may be helpful in the interpretation of the malformations observed in the caudal regression syndrome. In the literature, often the secondary neurulation process is mentioned as the onset of morphologic derailment (1, 5, 13, 14, 16). However, the majority of patients in the present study showed agenesis of parts of the caudal spinal cords, spinal ganglia, and spines, all structures derived from the process of primary neurulation (patients 1 to 13 in the Table) (17). This strongly suggests the primary neurulation process to be involved in the pathogenesis of this syndrome. Absence of the filum terminale, derived from the secondary neurulation process, would support this hypothesis. Unfortunately, MR does not allow adequate diagnosis of the filum terminale. Therefore, postmortem (neuro)pathologic and experi-



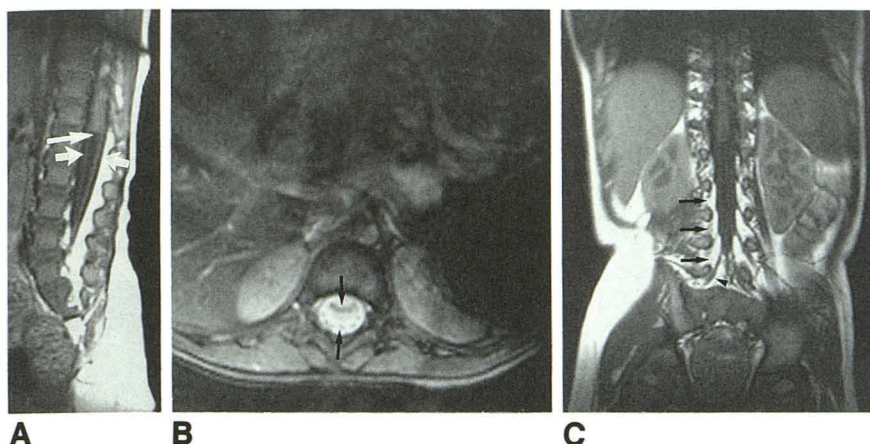


Fig. 6. Patient 5, a boy 1.4 years of age. A, Sagittal spin-echo T1-weighted image. The vertebral column terminates at S-1. The wedge-shaped cord terminus can be identified opposite T12 (*long arrow*). The separated anterior and posterior spinal roots of the cauda equina are clearly visible (*short arrows*).

B, Axial gradient-echo T2-weighted image well illustrates the separation of the anterior and posterior spinal roots (*arrows*). The liquor cerebrospinalis appears with high signal intensity on this sequence.

C, Coronal spin-echo T1-weighted image shows the high position of the cord terminus and the possible absence or hypoplasia of a number of lumbar roots at the right side (*arrows*), whereas the fifth lumbar root is present (*arrowhead*).

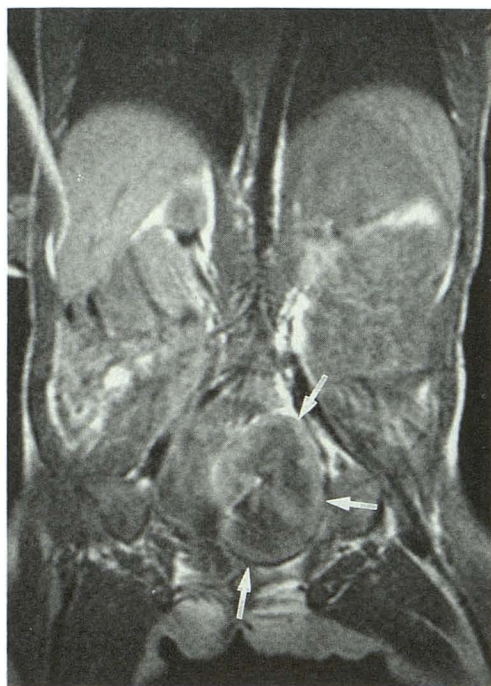


Fig. 7. Coronal spin-echo T1-weighted image in the same girl as Figure 2 (patient 15). It illustrates an associated genitourinary malformation, a renal ectopia. The left kidney is situated in the pelvic region (*arrows*).

mental animal studies shall be necessary to elucidate this problem.

A second group, patients 14 to 17, showed, beside caudal vertebral agenesis, tethered spinal cords with or without agenesis or dysgenesis of the cord termini. This combination of malformations has been described before in the literature (3, 26) and is best explained as resulting from derailment of the process of degeneration and differentiation of an initially normally developed primary and secondary neural tube, in combina-

tion with derailment of the differentiation of the mesenchymal vertebrae.

The minor vertebral defects in combination with a normal spinal cord, as observed in the patients 18 and 19, are also caused by a derailment of the differentiation process, but only concerning the chondrofication and bone centers of the mesenchymal vertebrae. Because the neural tube and filum terminale are not involved, these vertebral defects must be interpreted as isolated defects. From the embryologic point of view, these patients therefore should not be included in the group with caudal regression syndrome.

The interrelation between the spinal cord and spine malformations and the associated anomalies observed in this syndrome is probably best explained as follows. In the development of the primitive urogenital sinus and hindgut, the embryonic folding process, taking place during the primary neurulation process, plays an important role (27). This is mainly the result of the expansive longitudinal growth of both the neural groove and tube and the mesodermal compartment, the latter caused by cell deposition from the primitive streak and neural crest (27, 28). A disturbance of this folding process, including a nondisruption of the anal membrane caused by lack of cell death, can lead to the associated anomalies observed in the caudal regression syndrome (27).

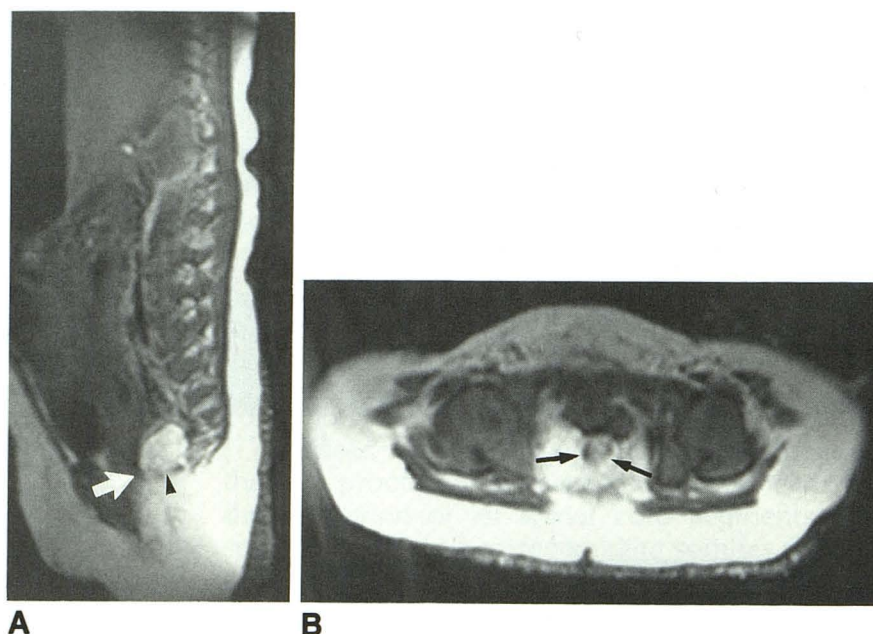
The cause of the caudal regression syndrome is largely unknown, but in approximately 16% the syndrome is associated with maternal diabetes (1, 2, 6, 8, 29). In the present study 4 of 19 children had diabetic mothers (patients 1, 2, 9, and 14). Insulin is often described as the possible teratogenic factor, although passage through the placental barrier of maternal insulin is not possi-



Fig. 8. Patient 7, a girl 3.5 months of age.

A, Sagittal spin-echo T1-weighted image with a high level of anal atresia (arrow). The vertebral column terminates at S-1, and a large (pre)sacral lipomatous mass is visible (arrowhead).

B, Axial spin-echo T1-weighted image through the pelvic region. Severe hypoplasia of the puborectal sling (arrows) is visible, surrounded by lipomatous tissue.



ble, and fetal insulin is not produced before the eighth week of development (30–33). In patients 1, 2, and 9 the malformations are most likely evoked during the primary neurulation process. Therefore, it is more likely that other factors related to diabetes, such as hyperglycemia and ketone bodies, are involved in these patients (31, 33).

In conclusion, to describe the pathogenesis of the caudal regression syndrome it seems necessary to divide the patients in two groups. In the first group, containing the majority of patients, the malformations are best explained as caused by a disturbance of the primary neurulation process (patients 1 to 13). The malformations observed in the second group are probably caused by derailment of the process of degeneration and differentiation of an initially normally developed primary and secondary neural tube (patients 14 to 17). The associated anomalies can be ascribed to involvement of both the neural tube and mesodermal compartment. Although MR contributes to a better insight in the morphology and, likewise, pathogenesis of congenital malformations, postmortem (neuro)pathologic examinations and experimental animal studies will remain necessary to determine the exact pathogenetic mechanisms involved.

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