# TREATMENT OF PATIENTS WITH CAUDAL REGRESSION SYNDROME: A SYSTEMATIC REVIEW OF THE LITERATURE

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**Objective.** To analyze and summarize the data of modern literature on the issues of surgical treatment and natural course of the spine and spinal cord pathology in patients with various types of caudal regression syndrome (CRS).

**Material and Methods.** A systematic review of the literature on the issue of treatment of the spine and spinal cord pathology in patients with CRS was performed. Selection criteria were: articles for the period 2002–2022, original studies of populations/patients with various forms of CRS with a description of treatment methods and long-term results of treatment or observation. A total of 28 articles on the treatment of various forms of CRS with the described results of treatment of 212 patients were analyzed: 29 patients with CRS in combination with open neural tube defects and 183 patients with closed forms of CRS. Evaluation criteria included number of patients, gender, type of spinal cord pathology, type of sacral agenesis, presence of the spine and lower extremities deformities, concomitant pathology, operations performed and their complications, and results.

**Results.** The studied patients underwent the following surgeries on the spine and spinal cord: untethering of the spinal cord, correction and stabilization surgeries on the spine, plasty of the spinal cord herniation, plasty of the terminal meningocele, and removal of the presacarial volumetric mass. The greatest number of complications occurred after operations on the spine and sacrum. The majority of patients (67 %) with sacral agenesis by the end of the follow-up period (average 14 years) walked independently or with the help of devices, and a minority of them (33 %) could not walk. More than half of patients with CRS (67 %) had a neurogenic bladder, urinary incontinence, or suffered from a chronic urinary tract infection. Fecal incontinence and constipation were less common (46 %).

**Conclusions.** Patients with CRS have a good potential for improvement/recovery of walking and pelvic organ dysfunction. This is extremely important to timely carry out multimodality treatment of patients with CRS who have neurosurgical, orthopedic, urogenital and colorectal problems in CRS, and to start early motor rehabilitation and physiotherapy.

**Key Worlds:** caudal regression syndrome, pathology of the spine and spinal cord, sacral agenesis, dysfunction of the pelvic organs.

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Caudal regression syndrome (CRS) involves the presence of partial or complete sacral agenesis, often with concomitant abnormalities of the pelvis, rectum, genitourinary system, lumbar spine, lower extremities, and caudal spinal cord [1]. Treatment of patients suffering from CRS is multimodal, including urological, surgical, neurosurgical and orthopedic techniques, often "crisscrossing" with each other [2, 3].

Malformations of the spinal cord in CRS include open defects of the neural tube (myelomeningocele, myeloschisis), lipomas of the medullary cone and terminal filament, split cord malformations, and cigar-shaped (blunt-ended) conus medullaris [4]. In most cases, neural tube defects are associated with congenital urination disorders caused by both myelodysplasia and tethered spinal cord syndrome. Additionally, urination disorders may be associated with concomitant malformations of the genitourinary system (for example, bladder exstrophy). Since CRS is often followed by malformations of the colorectal and genitourinary systems, the treatment strategy is not always clear. Myelodysplasia, tethered spinal cord syndrome, asymmetry of the lower extremities, vertebral malformations, asymmetric pathology of the sacroiliac joints – all this can equally cause aggravation of deformities of the lower extremities and scoliosis.

The main questions of this study are: What is the long-term results of treatment and follow-up of patients with CRS? How can we improve their functional status and satisfaction with life?

The objective is to analyze and summarize the data from modern literature on the issues of surgical treatment and the natural course of the spine and spinal cord pathology in patients with various types of caudal regression syndrome (CRS).

## Material and Methods

A systematic review of the literature sources on the topic of CRS has been performed.

Selection criteria: papers for 2002–2022, original studies of groups of patients or patients with various forms of CRS with a description of treatment techniques and long-term results.

The search queries used in Russian and English were as follows: caudal

regression syndrome, sacral agenesis, Currarino syndrome. The search was performed on the eLibrary, Google Scholar, and PubMed databases.

A total of 241 papers on CRS were found during the analysis of the literature. Reviews, analytical articles, expert opinions, duplicates, animal studies, articles without descriptions of treatment techniques and results, as well as ones without a minimum follow-up period, were removed from their number. Finally, 28 publications on the treatment of various kinds of CRS were chosen, each of which describes the outcomes of treatment for 212 patients: 97 (46 %) male and 115 (54 %) female.

Evaluation criteria: number of patients, gender, type of spinal cord pathology, type of sacral agenesis, presence of spinal deformity, concomitant pathology, procedures performed and their complications, outcomes.

## Results

*General information and natural course*

Out of 212 described patients, 29 (14 %) had CRS in combination with open neural tube defects [5, 6]; 183 (86 %) had closed forms of CRS [2, 5–29] (Table 1). Hemisacrum (Renshaw I, Pang IV types of sacral agenesis) was reported in 66 (31 %) patients; partial sacral agenesis below S1 (Renshaw II, Pang III) was reported in 95 (45 %); complete sacral or lumbosacral agenesis (Renshaw III–IV, Pang II) was reported in 51 (24 %). A cigar-shaped conus medullaris was met in 26 (12 %) cases; tethered spinal cord syndrome associated with a closed neural tube defect was met in 42 (20 %); Currarino syndrome (at least 2 of the following signs: sacral agenesis, presacral mass, and anorectal malformation) was met in 16 (8 %); VACTERL-association (at least 3 of the mandatory signs) was met in 11 (5 %); and sirenomelia was detected in 3 (1.4 %).

Three patients with Currarino syndrome suffered spontaneous acute meningitis and intradural abscesses with the onset of paraparesis [9, 16, 18].

Hydrocephalus was reported in 15 cases, associated mainly with open neural tube defects (Table 2). Spinal deformities included scoliosis (84 patients) and pathological kyphosis (39 patients). 41 patients suffered from pathology of the femoral joints, 16 of the knee joints, 62 of the ankle joints and deformity of the feet, and 25 had a considerable difference in the length of the extremities. Anorectal malformations, including proctatresia and stenosis, were in 69 patients; genitourinary system anomalies were in 61; and cardiac defects were in 15.

*Surgical treatment*

Most patients with CRS underwent the following procedures on the spine and spinal cord: untethering of spinal cord [19, 20, 30], spinopelvic fixation, correction of sacroiliac dislocation or correction of spinal deformity [11, 21, 23–26, 30, 31], plasty of congenital spinal cord herniation [5, 6], plasty of terminal meningocele, or removal of a presacral volumetric mass [9, 16, 28, 29].

Correction of lower extremity abnormalities [21, 23, 24, 31], colorectal procedures [5, 6, 8, 9, 20, 28, 31], genitourinary system surgeries [5, 6, 8, 9, 19, 20, 28] and heart surgeries [2, 5, 6, 8, 10, 28, 31] were all performed concurrently (Table 3). Only 4 of the 212 patients did not have any procedures during the follow-up period.

In the first days of life, patients with CRS underwent the following procedures: plasty of a congenital spinal cord herniation with cerebrospinal fluid leakage and a colorectal surgery. The second line was surgeries for hydrocephalus (in the first months of life in patients with open spinal dysraphism) and cystic forms of meningomyelo- or meningocele without cerebrospinal fluid leakage (usually during the first year of life). After a year, secondary colorectal plasty and reconstruction of the bladder and urethra were performed. Orthopedic procedures and spinal cord untethering were typically initiated at the age of two years old and continued until the end of active growth. After puberty, there is insufficient data on surgeries in the literature; the mean age at the end of follow-up period is 170 months (14 years).

*Complications*

The number of complications described in spinal cord untethering in CRS is relatively insignificant (70 procedures of untethering in CRS are described in Table 3). Gills et al. [12] reported a total of 6 complications, namely problems with wound repair, traumatic cerebrospinal fluid leakage, and wound infection.

The greatest number of complications arose after surgeries on the spine and sacrum (Table 4): 47 complications after 109 procedures [5, 6, 8, 10–15, 20, 21, 23–27, 32]. The most frequent complication was the nonunion of the bone block, especially with complete sacral agenesis and lumbosacral agenesis (18 (54 %) cases), followed by infection of the surgical site (10 (30 %) cases), traumatic cerebrospinal fluid leakage (3 (9 %) cases), and other problems with wound repair (2 (6 %) cases).

*Treatment outcomes*

Data on the functional status (FIM/weeFIM) of patients with CRS were presented by Baleo lu et al. [5] in 2016. They compared the functional status among 38 patients suffering from CRS in combination with open spinal dysraphism and closed forms of CRS: on average, FIM was 92 and 109 at the age of 10 years, respectively.

According to the publications, the majority of patients with sacral agenesis eventually walked independently or with the help of devices – 118 (67%) out of 176 described cases; and a minority of them could not walk – 58 (33 %) out of 176 (Table 4). During treatment, patients with CRS often have improvements in the function of the lower extremities and bladder control.

According to the analysis of the literature, it can be concluded that more than half of the patients with CRS had neurogenic bladder, urinary incontinence or suffered from chronic urinary tract infection (121 (67 %) of the 180 described cases; Table 4). Less frequently reported conditions were fecal incontinence or constipation, which were most prevalent in patients with open neural tube abnormalities in combination with CRS or in those who had undergone colorectal surgeries (68 (46 %) of 148 described cases; Table 4).

Table 1
Characteristics of patients with caudal regression syndrome (according to the literature), n

| Author | Year | Patients | Male | Female | Types of sacral agenesis | | | ONTD | Cigar-shaped cone | SCT + CNTD | Currarino syndrome | VACTERL | Sirenomelia |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Renshaw I/ Pang IV | Renshaw II/ Pang III | Renshaw III–IV/ Pang I–II | | | | | | |
| Balioğlu et al. [5] | 2016 | 38 | 13 | 25 | 19 | 15 | 4 | 19 | NA | 4 | 0 | 4 | 1 |
| Bray et al. [7] | 2017 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Caird et al. [8] | 2007 | 16 | 10 | 6 | 1 | 4 | 11 | 9 | NA | NA | 0 | 1 | 0 |
| Emami-Naeini et al. [6] | 2010 | 50 | 24 | 26 | 14 | 31 | 5 | 0 | 11 | NA | 0 | 1 | 0 |
| Esposito et al. [10] | 2022 | 6 | 5 | 1 | 0 | 0 | 6 | 0 | 6 | 0 | 0 | 2 | 2 |
| Ferland et al. [11] | 2015 | 6 | 3 | 3 | 3 | 0 | 3 | 0 | NA | NA | 0 | NA | 0 |
| Gillis et al. [12] | 2013 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Graul et al. [13] | 2019 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Griffet et al. [14] | 2010 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 |
| Kanbara et al. [15] | 2020 | 2 | 2 | 0 | 0 | 0 | 2 | 0 | NA | 0 | 0 | 0 | 0 |
| Kang et al. [17] | 2021 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 |
| Kansal et al. [18] | 2011 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 |
| Kilickesmez et al. [19] | 2006 | 2 | 1 | 1 | 0 | 2 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| Martucciello et al. [20] | 2004 | 6 | 1 | 5 | 5 | 1 | 0 | 0 | NA | 4 | 0 | 0 | NA |
| Zhang et al. [26] | 2018 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Mesa et al. [21] | 2011 | 5 | 2 | 3 | 5 | 0 | 0 | 0 | NA | NA | 0 | 0 | 0 |
| Morimoto et al. [22] | 2015 | 2 | 0 | 2 | 0 | 2 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| Salsi et al. [23] | 2020 | 1 | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 |
| Sen et al. [2] | 2007 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 0 |
| Szumera et al. [24] | 2018 | 2 | 1 | 1 | 0 | 0 | 2 | 0 | 2 | 0 | 0 | 0 | 0 |
| Vissarionov et al. [25] | 2019 | 12 | 8 | 4 | 0 | 0 | 12 | 0 | NA | NA | 0 | NA | 0 |
| Zhang et al. [27] | 2021 | 24 | 14 | 10 | 18 | 6 | 0 | 0 | NA | 0 | 0 | NA | 0 |
| Cearns et al. [9] | 2018 | 10 | 4 | 6 | 0 | 10 | 0 | 0 | 0 | 10 | 10 | 0 | 0 |
| Isik et al. [16] | 2009 | 4 | 2 | 2 | 0 | 4 | 0 | 0 | 0 | 4 | 4 | 0 | 0 |
| Kemp et al. [29] | 2014 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 |
| Lee et al. [28] | 2012 | 14 | 4 | 10 | 0 | 14 | 0 | 0 | 0 | 12 | 0 | 1 | 0 |
| Kolesov et al. [30] | 2016 | 2 | 0 | 2 | 0 | 0 | 2 | 0 | 1 | 1 | 0 | 0 | 0 |
| Semenov et al. [31] | 2014 | 1 | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 1 | 0 |
| Total | – | 212 | 97 | 115 | 66 | 95 | 51 | 28 | 26 | 42 | 16 | 11 | 3 |

ONTD – open neural tube defect; SCT – spinal cord tethering; CNTD – closed neural tube defects; VACTERL – Vertebral anomalies, Anal atresia, Cardiac malformations, Trachea-Esophageal fistula, Renal anomalies and Limb abnormalities; NA – not available.

Table 2
Concomitant pathologies in patients with caudal regression syndrome (according to the literature), n

| Author | Year | Patients | HC | Scoliosis | Pathological kyphosis | Pathology of the hip joint | Pathology of the knee joint | Pathology of the ankle joint | Significant difference in extremities length | Anorectal malformation | Malformation of the genitourinary system | Heart defect |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Balioğlu et al. [5] | 2016 | 38 | 8 | 23 | 20 | 20 | 4 | 21 | 15 | 23 | 24 | 8 |
| Bray et al. [7] | 2017 | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 1 | 0 |
| Caird et al. [8] | 2007 | 16 | 1 | 5 | NA | 0 | 0 | 6 | 0 | 2 | 9 | 1 |
| Emami-Naeini et al. [6] | 2010 | 50 | 4 | 13 | NA | 1 | NA | 1 | NA | 11 | 2 | 2 |
| Esposito et al. [10] | 2022 | 6 | 0 | 2 | 0 | 1 | 0 | 4 | 0 | 1 | 4 | 1 |
| Ferland et al. [11] | 2015 | 6 | 0 | 4 | 4 | NA | NA | NA | NA | NA | NA | NA |
| Gillis et al. [12] | 2013 | 1 | 0 | 1 | 0 | NA | NA | 1 | 0 | 1 | 1 | 0 |
| Graul et al. [13] | 2019 | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Griffet et al. [14] | 2010 | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 |
| Kanbara et al. [15] | 2020 | 2 | 1 | 2 | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 0 |
| Kang et al. [17] | 2021 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 |
| Kansal et al. [18] | 2011 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Kilickesmez et al. [19] | 2006 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 1 | 0 |
| Martucciello et al. [20] | 2004 | 6 | 0 | 1 | NA | NA | NA | NA | NA | 6 | 5 | 0 |
| Zhang et al. [26] | 2018 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Mesa et al. [21] | 2011 | 5 | 0 | 5 | 0 | 0 | 0 | 5 | 4 | NA | NA | NA |
| Morimoto et al. [22] | 2015 | 2 | 0 | 0 | 0 | 2 | 0 | 0 | 2 | 0 | 0 | 0 |
| Salsi et al. [23] | 2020 | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 0 | 1 | 0 |
| Sen et al. [2] | 2007 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 1 | 1 |
| Szumera et al. [24] | 2018 | 2 | 0 | 1 | 2 | 1 | 2 | 2 | 0 | 0 | 1 | 0 |
| Vissarionov et al. [25] | 2019 | 12 | 0 | 0 | 12 | 11 | 7 | 12 | NA | NA | NA | NA |
| Zhang et al. [27] | 2021 | 24 | 0 | 24 | NA | NA | NA | NA | NA | NA | NA | NA |
| Cearns et al. [9] | 2018 | 10 | 0 | NA | NA | NA | NA | NA | NA | 6 | 4 | 0 |
| Isik et al. [16] | 2009 | 4 | 1 | NA | NA | 0 | 0 | 1 | 0 | 4 | 0 | 0 |
| Kemp et al. [29] | 2014 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Lee et al. [28] | 2012 | 14 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 8 | 6 | 1 |
| Kolesov et al. [30] | 2016 | 2 | 0 | 0 | 0 | 0 | 1 | 2 | 0 | 0 | 0 | 0 |
| Semenov et al. [31] | 2014 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 1 | 0 | 1 |
| Total | — | 212 | 15 | 84 | 39 | 41 | 16 | 62 | 22 | 69 | 61 | 15 |

HC — hydrocephalus; NA — not available.

Chronic pain in the legs or back with CRS was rarely described in children; it was more common in adult patients [8, 12, 18, 22, 26].

The analyzed sources present 7 cases of mental retardation in CRS, almost all for unknown reasons [8, 9, 17].

## Discussion

*Etiology of the CRS*

A number of studies have described possible modifiable trigger mechanisms for the development of CRS: high doses of retinoic acid, hyper- and hypoglycemia, hypoxia, the use of diethylpropion hydrochloride and hormonal imbalance [4]. For example, one of the studies showed that CRS has an incidence of 1 in 10,000 live births in the general population and 1 in 350 in mothers with gestational diabetes mellitus [4]. Moreover, the literature describes sacral agenesis in chromosomal aberrations, for example, in 8p11.2 deletion, 7q36 deletion [33, 34], 3q26.32-q27.2 duplication [35], 19q trisomy and 7q monosomy [13].

A connection was found with mutations in the MNX1 gene in Currarino syndrome. When reviewing the Currarino syndrome cases, it should be noted that the majority of them contain sacral agenesis below S1, an anterior sacral defect with presacral lesion (meningocele, teratoma, etc.), spinal cord tethering by distal lipomas, and anal stenosis or proctatresia [9, 16, 28, 29]. Parents should be informed by a doctor regarding a possible autosomal dominant mode of inheritance in cases if they or their children have signs of Currarino syndrome.

There are other genes whose mutations may be responsible for the formation of caudal agenesis: *VANGL1, HOXD13, CDX2, TBXT* and *PTEN* [36, 37]. Variants of *VANGL1* result in Klippel-Feil syndrome in combination with CRS [38]. The literature describes a combination of VACTERL association (the presence of at least three anomalies: spine, anorectal malformation, heart defect, tracheoesophageal abnormality, kidney and extremities abnormalities) with CRS [39, 40].

*Surgical treatment of CRS*

The sequence of procedures for various forms of CRS is quite obvious. Firstly, surgeries are performed to prevent life-threatening complications. For example, early plasty of spinal cord herniation with cerebrospinal fluid leakage is done on the first day of life and is aimed at preventing meningitis, and surgeries for proctatresia prevent the onset of intestinal obstruction and peritonitis on the first day of life.

Performing early preventive spinal cord untethering is a controversial issue since early preventive procedures (without symptoms of a tethered spinal cord syndrome) may result in the need for repeated surgery in the future with an increased risk of complications. It is better to wait until the age of 2 years, when it is possible to evaluate whether the child has difficulties with sitting, neurological and urological disorders, or progressive deformity of the spine, which can also arise due to tethered spinal cord syndrome. Exceptions to this norm are presacral volumetric lesion [9, 16], signs of neurenteric sinuses or cysts, dermoid cysts, and dermal sinus [18], thin skin of meningocystocele or myelomeningocystocele with a high risk of injury and cerebrospinal fluid leakage, and progressive growth of meningocystocele or myelomeningocystocele. It is recommended to perform surgeries in all these cases in the first months of life.

*Complications*

Generally, the number of procedures under general anesthesia in patients with various forms of CRS during their lifetime is quite large. The bailout plan may be to reduce them by performing two-in-one or three-in-one surgeries. Nevertheless, as practice has shown, this approach is associated with a high risk of complications [41].

One more challenging point is the consideration of complications. Should the following conditions be considered as complications: progression of spinal deformity above the level of instrumentation or progression of deformity of the lower extremities after orthopedic procedures; secondary spinal cord tethering after plasty of an open neural tube defect; repeated spinal cord tethering after primary untethering; anal restenosis requiring dilation after anorectoplasty? All of these situations are likely to be considered as complications since good documentation (type of abnormality, nature and features, age at the time of the primary surgery) can help identify factors contributing to the need of repeated surgeries.

*Treatment outcomes and the natural course of the disease*

Since three cases of spontaneous acute meningitis and intradural abscesses with the onset of paraparesis have been described in the literature [9, 16, 18], it is worth highlighting the critical nature of early surgical treatment of patients with closed forms of CRS in combination with presacral volumetric lesions, suspected neurenteric sinuses or cysts, dermoid cysts or dermal sinuses.

The treatment results in improvement of functional status, walking and urologic symptoms in patients with CRS. This highlights the significance of timely treatment of patients with neurosurgical and orthopedic disorders. Early motor rehabilitation, remedial gymnastics and timely orthopedic support are critical in preparing these children for adulthood [3, 42].

CRS-associated urological disorders can be caused by a tethered spinal cord syndrome, underdevelopment of the medullary cone, myelodysplasia, concomitant urogenital malformations and hypoplasia of the nerves responsible for urination control. All children with CRS are recommended to be followed up by an urologist; they should undergo periodic urodynamic examinations and renal ultrasound.

Fecal incontinence or constipation in CRS can be caused by anal restenosis, Hirschsprung's disease, or a lack of innervation of the caudal colon (a combination with CRS is hardly described). However, they can also be a manifestation of tethered spinal cord syndrome, and there are reports of improvement after the untethering procedure in the literature.

Chronic back and leg pain can manifest in patients with CRS as a result of tethered spinal cord syndrome, spinal

Table 3
Surgeries performed on patients with caudal regression syndrome (according to the literature), n

| Author | Year | Patients | ONTD plasty | Spinal cord untethering | VPS | Surgery on legs | Spine and/or pelvic surgery | Colorectal surgery | Genitourinary surgery | Heart surgeries |
|---|---|---|---|---|---|---|---|---|---|---|
| Balioğlu et al. [5] | 2016 | 38 | 20 | 13 | 8 | 21 | 33 | NA | NA | NA |
| Bray et al. [7] | 2017 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Caird et al. [8] | 2007 | 16 | 0 | NA | 1 | 4 | 5 | 2 | 10 | 1 |
| Emami-Naeini et al. [6] | 2010 | 50 | 9 | 19 | 4 | NA | 13 | 11 | 2 | 2 |
| Esposito et al. [10] | 2022 | 6 | 0 | 0 | 0 | 3 | 2 | 1 | 8 | 0 |
| Ferland et al. [11] | 2015 | 6 | 0 | NA | NA | NA | 4 | NA | NA | NA |
| Gillis et al. [12] | 2013 | 1 | 0 | 1 | 0 | 0 | 1 | 1 | 1 | 0 |
| Graul et al. [13] | 2019 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Griffet et al. [14] | 2010 | 1 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| Kanbara et al. [15] | 2020 | 2 | 0 | 0 | 1 | 0 | 2 | 2 | 0 | 0 |
| Kang et al. [17] | 2021 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Kansal et al. [18] | 2011 | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| Kilickesmez et al. [19] | 2006 | 2 | 0 | 2 | 0 | 0 | 0 | 3 | 0 | 0 |
| Martucciello et al. [20] | 2004 | 6 | 0 | 4 | 0 | NA | 1 | 8 | 2 | 0 |
| Zhang et al. [26] | 2018 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Mesa et al. [21] | 2011 | 5 | 0 | NA | NA | 0 | 5 | NA | NA | NA |
| Morimoto et al. [22] | 2015 | 2 | 0 | 2 | 0 | 4 | 0 | 0 | 0 | 0 |
| Salsi et al. [23] | 2020 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| Sen et al. [2] | 2007 | 1 | 0 | 0 | 0 | 1 | 0 | 2 | 0 | 0 |
| Szumera et al. [24] | 2018 | 2 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| Vissarionov et al. [25] | 2019 | 12 | 0 | NA | NA | NA | 12 | NA | NA | NA |
| Zhang et al. [27] | 2021 | 24 | 0 | 0 | 0 | NA | 24 | NA | NA | NA |
| Cearns et al. [9] | 2018 | 10 | 0 | 10 | 0 | NA | NA | 4 | 0 | 0 |
| Isik et al. [16] | 2009 | 4 | 0 | 4 | 1 | 0 | NA | 4 | 0 | 4 |
| Kemp et al. [29] | 2014 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Lee et al. [28] | 2012 | 14 | 0 | 12 | 0 | 0 | 0 | 8 | 0 | 8 |
| Kolesov et al. [30] | 2016 | 2 | 0 | 1 | 0 | NA | 2 | 0 | 0 | 0 |
| Semenov et al. [31] | 2014 | 1 | 0 | 0 | 0 | 2 | 1 | 1 | 0 | 1 |
| Total | — | 212 | 29 | 70 | 15 | 39 | 109 | 48 | 23 | 16 |

ONTD — open neural tube defect; VPS — ventriculoperitoneal shunting; NA — not available.

Table 4
Complications and results of treatment of patients with caudal regression syndrome (according to the literature), n

| Author | Year | Patients | Complications of neurosurgical procedures | Complications of spinal surgeries | Complications of leg surgeries | Other complications | Age at the end of follow-up, months | DPMD | Chronic pain | Does not walk | Walk | NB/UI/CUI | Fecal incontinence or constipation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Balioğlu et al. [5] | 2016 | 38 | NA | 15 | 1 | NA | 121 | 0 | NA | 10 | 28 | 24 | 23 |
| Bray et al. [7] | 2017 | 1 | 0 | 0 | 0 | 0 | 36 | 0 | 0 | 0 | 1 | 0 | 0 |
| Caird et al. [8] | 2007 | 16 | NA | 0 | 0 | NA | 173 | 4 | 10 | 0 | 16 | 16 | NA |
| Emami-Naeini et al. [6] | 2010 | 50 | 0 | NA | NA | NA | 72 | NA | 2 | 23 | 21 | 30 | 12 |
| Esposito et al. [10] | 2022 | 6 | 0 | 0 | 0 | 0 | 163 | NA | NA | 5 | 1 | 6 | 6 |
| Ferland et al. [11] | 2015 | 6 | NA | 10 | NA | NA | 156 | NA | NA | 3 | 3 | NA | NA |
| Gillis et al. [12] | 2013 | 1 | 5 | 0 | 0 | 0 | 432 | 0 | 1 | 0 | 1 | 1 | 1 |
| Graul et al. [13] | 2019 | 1 | 0 | 1 | 0 | 0 | 220 | 0 | 0 | 0 | 1 | 0 | 0 |
| Griffet et al. [14] | 2010 | 1 | 0 | 1 | 0 | 0 | 168 | 0 | 0 | 1 | 0 | 1 | 1 |
| Kanbara et al. [15] | 2020 | 2 | 0 | 3 | 0 | 0 | 170 | NA | NA | 1 | 1 | NA | NA |
| Kang et al. [17] | 2021 | 1 | 0 | 0 | 0 | 0 | 60 | 1 | 0 | 0 | 1 | 1 | 1 |
| Kansal et al. [18] | 2011 | 1 | 1 | 0 | 0 | 0 | 540 | 0 | 1 | 0 | 1 | 0 | 1 |
| Kilickesmez et al. [19] | 2006 | 2 | 0 | 0 | 0 | 0 | 78 | 0 | 0 | 0 | 2 | 1 | 2 |
| Martucciello et al. [20] | 2004 | 6 | NA | NA | NA | 0 | 140 | NA | NA | NA | NA | 3 | 4 |
| Zhang et al. [26] | 2018 | 1 | 0 | 0 | 0 | 0 | 144 | 0 | 1 | 0 | 1 | 0 | 0 |
| Mesa et al. [21] | 2011 | 5 | NA | 1 | 0 | NA | 233 | NA | NA | 0 | 5 | 5 | 0 |
| Morimoto et al. [22] | 2015 | 2 | 0 | 0 | 0 | 0 | 192 | 0 | 2 | 0 | 2 | 0 | 0 |
| Salsi et al. [23] | 2020 | 1 | 0 | 1 | 0 | 0 | 384 | NA | NA | 1 | 0 | 1 | 1 |
| Sen et al. [2] | 2007 | 1 | 0 | 0 | 0 | 0 | 48 | 0 | 0 | 0 | 1 | 1 | 1 |
| Szumera et al. [24] | 2018 | 2 | 0 | 3 | 0 | 0 | 192 | NA | NA | 2 | 0 | 2 | 2 |
| Vissarionov et al. [25] | 2019 | 12 | NA | 5 | NA | NA | 48 | NA | NA | 12 | 0 | 12 | 12 |
| Zhang et al. [27] | 2021 | 24 | 0 | 7 | NA | NA | 166 | NA | NA | NA | NA | NA | NA |
| Cearns et al. [9] | 2018 | 10 | 1 | 0 | NA | 0 | 79 | 2 | 0 | 0 | 10 | 5 | 6 |
| Isik et al. [16] | 2009 | 4 | 1 | 0 | 0 | 0 | 71 | 0 | NA | 0 | 4 | 0 | 0 |
| Kemp et al. [29] | 2014 | 1 | 0 | 0 | 0 | 0 | 180 | 0 | 0 | 0 | 1 | 1 | 0 |
| Lee et al. [28] | 2012 | 14 | 0 | 0 | 0 | 0 | 120 | NA | NA | 0 | 14 | 10 | NA |
| Kolesov et al. [30] | 2016 | 2 | 0 | 0 | NA | NA | 114 | 0 | 1 | 0 | 2 | 2 | NA |
| Semenov et al. [31] | 2014 | 1 | NA | 0 | 0 | 0 | NA | 0 | 0 | 0 | 1 | 1 | 1 |
| Total | — | 212 | 8 | 47 | 1 | 0 | 170 (mean) | 7 | 18 | 58 | 118 | 121 | 68 |

DPMD — delayed psychomotor development; NB — neurogenic bladder; UI — urinal incontinence; CUI — chronic urinal infection; NA — not available.

deformity, spinosacral instability, leg deformities and an uneven load on the joints. More frequently, pain occurs with age. In cases of isolated pain, it is better to start treatment and examination with a course of anesthetics (including gabapentin and clonazepam).

Another relevant symptom is mental retardation, which can be associated with hypoxic-ischemic brain injury, genetic mutations, and other factors that have toxic effects on the fetus and a newborn. Cognitive impairments affect functional independence and letter grades. In this regard, they also need to be considered in the clinical evaluation and planning of procedures to improve outcomes.

## Conclusion

Patients with diagnosed sacral agenesis or suspected sacral agenesis in utero should have a chromosomal analysis, as well as analysis for the following gene mutations: *MNX1* gene, *VANGL1, HOXD13, CDX2, TBXT* and *PTEN*.

In cases of the birth of a patient with CRS, first of all, it is required to perform procedures to prevent life-threatening complications: early plasty of open defects of the neural tube with cerebrospinal fluid leakage and surgeries for proctatresia (the first day of life). Surgery is recommended during the first months of life in all the following cases: urological and cardiological procedures, removal of presacral lesions, surgeries for neuroenteric sinuses or cysts, removal of dermoid cysts and dermal sinuses. Early preventive spinal cord untethering is controversial. Early surgeries may result in the need for reoperations in the future, with an increased risk of complications. Orthopedic surgeries and untethering surgeries in CRS should not be conducted on children under the age of two. It is hazardous to decrease the number of surgeries per child by performing combined surgeries (two-in-one and three-in-one). This raises the risk of complications, especially with simultaneous spinal cord untethering and spinal deformity correction. It is wiser to divide the procedures by time. Since the risk of bone block nonunion in CRS is very high, it is advised to use autogenous bone grafts in addition to screws and, if required, pay attention to anterior fusion.

More than 60 % of patients with sacral agenesis can walk independently or with devices. It is important to solve CRS-associated neurosurgical and orthopedic challenges in time and to begin early motor rehabilitation and remedial gymnastics. The provision of lower extremities orthoses, if necessary, is a major influence in the process of preparing this group of children for adulthood.

All children with CRS are recommended to be followed up by an urologist; they should undergo periodic urodynamic examinations and renal ultrasound. Fecal incontinence or constipation in CRS can be caused by anal restenosis, Hirschsprung's disease, or a lack of caudal colon innervation, and it can also be a symptom of tethered spinal cord syndrome. The improvement of colon function after spinal cord untethering has been reported in the literature.

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