

Currarino Syndrome: Proposal of a Diagnostic and Therapeutic Protocol

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Background/Purpose: The Currarino syndrome (CS) is a peculiar form of caudal regression syndrome (CRS) characterized by the association of hemisacrum, anorectal malformation (ARM), and presacral mass. The authors analyzed retrospectively their series, and they propose a multidisciplinary diagnostic and therapeutic protocol that until now has not been introduced.

Methods: A series of 6 patients with CS is presented. Five of them were treated initially in other centers. None of them had an early diagnosis. All presented associated anomalies; in 50%, Hirschsprung's disease (HD) and other dysganglionoses were present. One patient died of a presacral ectopic nephroblastoma.

Results: Depending on the expressivity, 3 types of CS can be identified, complete, mild, and minimal. Dysganglionoses

and HD can be considered part of CS. A multidisciplinary diagnostic and therapeutic protocol is presented. Main points are sacrum x-Ray, molecular genetic diagnosis, radiologic evaluation of every member of CS families, magnetic resonance (MR) evaluation of patient spine and pelvis, suction rectal biopsies, and search for associated anomalies.

Conclusions: This protocol could give a valid contribution to the treatment of CS, allowing an early diagnosis and proposing a rational timing of multidisciplinary surgical procedures. Early diagnosis and treatment are essential to avoid morbidity and mortality from an undiagnosed presacral mass. *J Pediatr Surg* 39:1305-1311. © 2004 Elsevier Inc. All rights reserved.

INDEX WORDS: Currarino syndrome, meningocele, sacrum, Hirschsprung's disease, Anorectal malformations.

IN PATIENTS with caudal regression syndrome (CRS), a variable degree of sacral hypoplasia is always present¹ in association with other anomalies. The different types of sacral agenesis have been described and classified²⁻⁴ into the following categories (Fig 1): (1) total sacral agenesis with normal or short transverse pelvic diameter and possible lack of some lumbar vertebrae, (2) total sacral agenesis without involvement of lumbar vertebrae, (3) subtotal sacral agenesis or sacral hypodevelopment (with S1 present), (4) hemisacrum, and (5) coccygeal agenesis.

In 1981 Guido Currarino, a pediatric radiologist, described the triad of hemisacrum, anorectal malformation (ARM), and presacral mass.⁵ The radiologic aspect of sacrum described by Currarino is the so called "scimitar sign" (Fig 2). The most frequent type of rectal anomaly in Currarino syndrome (CS) is ARM with rectoperineal fistula, according to Peña classification.⁶ The same anomaly sometimes is described by other investigators as anorectal stenosis.⁷ However, different types of ARM can be present in CS (rectourethral fistula, rectovestibu-

lar fistula, rectocloacal fistula). The presence of rectoperineal fistula is related to difficult passage of stools and constipation.

The presacral mass can be an anterior meningocele (AM), a teratoma, a dermoid cyst, a rectal duplication, a combination, or another uncommon tumor.

CS has a great phenotype variability.⁸ Actually, many cases present asymptomatic hemisacrum without other anomalies, whereas others present a complete spectrum of malformations and other associated anomalies. Among neural tube defects (NTD), tethered cord or lipoma are common isolated or in association with AM.⁹

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0022-3468/04/3909-0001\$30.00/0

doi:10.1016/j.jpedsurg.2004.05.003

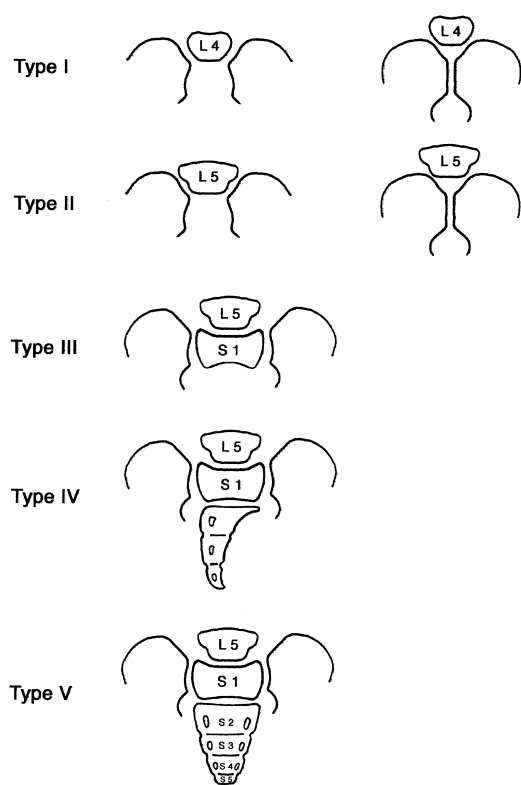


Fig 1. Sacral anomalies, according to the classifications of Kalitzk,² Pang,³ and Cama.⁴

Urologic involvement may be characterized by duplex ureter, horseshoe or duplex kidney, vesicoureteric reflux (VUR), dysplastic kidney, or hypospadias. Gynecologic malformations include bicornuate uterus, septate vagina, and bifid clitoris.^{10,11} Other sporadic associations of CS with Down's syndrome, and cranial and central nervous anomalies have been described.¹⁰ Given this great variability, the name of *Currarino syndrome*^{10,12} is more appropriate than Currarino triad.

CS is a genetic disease, with autosomal dominant inheritance. Different studies^{13,14} showed an important locus on chromosome 7 involved in normal sacral and anorectal development. In 2000, a causative gene for CS was identified as the *HLXB9* homeobox gene on chromosome 7q36¹⁰ by testing blood samples of 10 patients from different centers. Of these 10 patients studied by our group,¹⁰ 4 harbored point mutations on the *HLXB9* gene, whereas 3 showed a hemizygous deletion of the entire sequence. The same gene was tested in patients with other aspects of CRS, and no mutations were found.¹⁰ Consequently, from a clinical and molecular point of view, it is possible to conclude that CS is a particular type of CRS, with both a distinct sacral anom-

aly (the presence of hemisacrum), and genetic condition (mutations in *HLXB9* gene).

The real incidence of CS is not well defined. Early diagnosis is important to avoid life-threatening complications related to an unrecognized presacral mass, like meningitis, dystocia, compression or rupture of AM during delivery, or malignant transformation. Surgical approach to CS is multidisciplinary because it involves the neurosurgeon and the general surgeon,¹⁵ and different strategies can be adopted, depending on clinical presentation and phenotype expressivity. Many reports on the diagnosis and treatment of CS are present in the international literature, but they consider only particular cases or single aspects of this complex and clinically multiform syndrome. Moreover, there is no consensus on an international diagnostic and therapeutic protocol. In this report we present our series and, on the basis of our experimental¹⁰ and clinical experience, we propose a complete diagnostic and therapeutic approach to the syndrome.

MATERIALS AND METHODS

Our series includes 6 patients (5 girls and 1 boy) admitted to Gaslini Institute, Genoa, Italy, from 1993 to 2000 (Table 1). Five of them were observed after treatment in other centers.

Case 1

A baby girl born with ARM and rectoperineal fistula was initially treated in another institution. In the first month of life she underwent repeated dilations. Severe left VUR was identified, and she was operated on at 6 months of life. The child was affected by severe constipation, and ultrasound (US) and magnetic resonance (MR) examinations showed an AM that was operated on at 3 years of age. She was first referred to our department at 7 years of age for MR evidence of an AM that had increased in size, associated with tethered cord and small hydromielia. Clinically, she complained of constipation and encopresis. Sacrum x-Ray was pathognomonic of CS. The diagnosis was confirmed by molecular genetic studies. For molecular genetic studies, a blood sample (5 mL for infants, 10 mL for older patients) was



Fig 2. The hemisacrum is a pathognomonic feature of CS. This was the sacrum of our case 3.

Table 1. Phenotype Characterization of CS Patients

Patient No.	Sex	Family	HLXB9 Mutation	Type of CS	ARM (Fistula)	AM	ENS Anomaly	Other Associated Anomalies
1	F	—	R295W	Complete	Perineal	+	HD	Tethered cord, hydromielia, VUR
2	F	+	HLBX9 del	Complete	Perineal	+	HD	Tethered cord, teratoma
3	F	+	234delG	Complete	Perineal	+	N.C. dysg	Tethered cord, caudal lipoma, VUR
4	F	—	Not evaluated	Mild	Vestibular	—		Tethered cord, Mayer-Rokitansky s., renal agenesis, costal anomalies
5	F	—	Not evaluated	Complete	Vestibular	—		Tethered cord, spinal lipoma, ectopic nephroblastoma, VUR, costal and dorsal vertebral anomalies
6	M	+	No mutations	Mild	Urethral	+		

Abbreviations: ENS, Enteric nervous system; HD, Hirschprung’s disease; N.C. dysg, not classifiable.

collected in a Falcon tube with 2.5 to 5 mL of ACD (acid citrate dextrose). After DNA extraction, *HLXB9* analysis was performed for the 3 exons of the gene. Double gradient-denaturing gradient gel electrophoresis (DG-DGGE)²⁶ was performed on exons 2 and 3. Patients with abnormal electrophoretic pattern should be analyzed by DNA sequencing.¹⁰ Exon 1 presents an extremely high melting profile, therefore, requiring direct sequencing for mutation analysis. In this patient, molecular genetic analysis of *HLXB9* found a point mutation with aminoacid substitution (R295W on exon 3/a of the *HLXB9* gene). Rectal suction biopsy showed associated HD, and contrast enema showed a dilated sigmoid. The child underwent neurosurgery for AM repair and detethering. After 7 months she underwent posterior sagittal anorectoplasty (PSARP) associated with resection of the short distal aganglionic tract through a combined laparotomic and perineal approach. At 5-year follow-up, she is totally continent.

Case 2

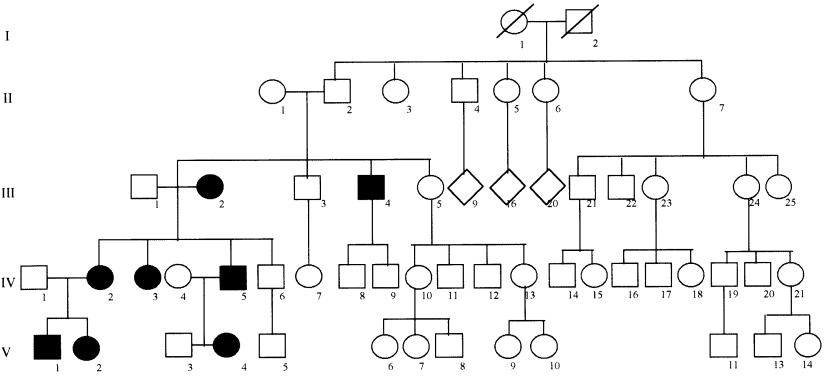
A baby girl born with ARM and narrow rectoperineal fistula presented with delayed meconium emission and constipation that continued during infancy. A maternal aunt and a cousin were affected by ARM (see familial tree, Fig 3). At 3 years of age she was referred to our surgical unit and underwent rectal suction biopsy, which showed increased acetylcholinesterase (AChE) fibers consistent with the diagnosis of HD. Left colostomy was done at 3 years of age followed after 4 months by PSARP with resection of the distal aganglionic tract. During surgery a presacral teratoma was found and resected, and an AM was diagnosed, which was repaired subsequently by the neurosurgeon together with detethering after 3 months. The diagnosis of familial CS was done after sacrum x-ray, which showed hemisacrum in both patient and relatives (Fig 3). Finally, the colostomy was closed. Molecular genetic studies found a complete deletion of *HLXB9* gene in all the affected cases (Fig 3).

Micturition cystourethrogram (MCU) results were negative. The patient presented mild constipation at follow-up. The postoperative suction rectal biopsy showed a normal innervation. Continence was optimal, and constipation disappeared completely at the last visit, 7 years after surgery.

Case 3

A baby girl born with ARM and rectoperineal fistula underwent PSARP in the first month of life. The postoperative period was complicated by infection and a perineal fistula. A right colostomy was done. The child was subsequently referred to our department, where a pelvic and spinal MR showed an AM, a caudal lipoma, and tethered cord. Neurosurgical treatment obtained AM repair and spinal cord detethering. The perineal fistula closed spontaneously, and the colostomy was closed at 1 year. During the follow-up, the patient presented severe constipation and fecal incontinence. X-ray showed hemisacrum (Fig 2). The parents underwent X-ray, and the mother presented a hemisacrum. Familial CS was diagnosed. Molecular genetic studies identified a 234delG of *HLXB9* gene in the patient and her mother. Pelvic MR in the mother was negative for presacral mass. The patient underwent rectal suction biopsy, the results of which showed a “not classifiable” dysganglionosis and negative findings for HD. A mild increase in AChE fibers was present in association with submucosal ganglia; the histochemical pattern did not meet Borchard criteria for intestinal neuronal dysplasia (IND).¹⁶ Contrast enema showed only a mild dilatation of the rectosigmoid. Anorectal manometry showed a hypotonic and asymmetric sphincter. Kidney US showed a mild right pelvic dilatation, and MCU showed bilateral vesicoureteral reflux (VUR), which was followed up conservatively. The patient was given laxatives and cleaning enema, but at 9 years of follow-up, constipation and incontinence improved only slightly.

Fig 3. The familial tree of our case 2. Black symbols are the relatives affected by CS. Our case 2 was patient V, 2. Her aunt (IV, 3) and cousin (V, 4) were affected by ARM; only hemisacrum was present in the patient’s mother (IV, 2), brother (V, 1), and uncle (IV, 5).



Case 4

A baby girl born with ARM and rectovestibular fistula, was treated elsewhere at birth with "cut-back" procedure. She had presented with scoliosis since the second year of life and agenesis of the left kidney. After menarche at 11 years of age, she presented with menstrual pain, and after a few months US examination showed a pelvic cystic dilatation to the left of the uterus. The patient was first referred to our surgical unit for abdominal and pelvic acute pain at 12 years of age. She did not present perineal body, and the anus was at the posterior margin of the vulva. Pelvic US and MR showed duplex uterus, left hematometra, and hematosalpinx. Left ovary was absent. The left uterus was blind ended (atresic left hemivagina), and right hemivagina was present. Sacrum x-ray showed a hemisacrum. Spinal MR showed a tethered cord. Accessory ribs (14 ribs bilaterally) were present on chest X-Ray. The parents did not have sacral anomalies. The diagnosis was sporadic CS associated with a variant of Mayer-Rokitansky-Küster-Hauser syndrome. The left hemiuterus was opened transvaginally, and a large amount (400 mL) of blood and serum was drained from left hemiuterus and hemisalpinx, which were removed 1 year later. PSARP was proposed, but the patient refused. She currently undergoes follow-up by the neurosurgeon for evaluation of the tethered cord. The family refused genetic studies.

Case 5

A baby girl born with ARM and rectovestibular fistula, underwent left colostomy in the first week of life, PSARP at 1 year, and colostomy closure 5 months later elsewhere. At 2.5 years of age she underwent neurosurgery for the exeresis of an intra-extradural lumbosacral lipoma. She was followed up for neurogenic bladder and bilateral VUR. She was first referred to our surgical unit at 4 years of age because of a large pelvic-perineal mass, rapidly increasing in volume. Sacrum x-ray showed a hemisacrum, while the parents did not present any anomalies, suggesting the diagnosis of sporadic CS. Multiple costal anomalies (fusions, 13 ribs bilaterally) and dorsal vertebral anomalies (hemivertebrae) were found at chest x-ray. MCU showed bilateral 4° VUR with a hypoplastic left kidney on US and Dimercaptosuccinic acid (DMSA) scintigraphy. Pelvic and medullary MR showed a huge mass occupying the whole pelvic cavity and extending inside the medullary canal (Fig 4). Thoracic computerized tomography (CT) showed multiple lung metastases.

The mass was biopsied and was found to be an ectopic neuroblastoma. Aggressive chemotherapy and radiotherapy were given with partial regression of the pelvic mass and complete regression of lung metastases, but after few months of treatment there was disease progression, and the child died at 4.9 years of age. Molecular genetic studies were not performed in this case.

Case 6

A man was operated on elsewhere at birth for ARM and rectourethral fistula. His father had a history of ARM with rectoperineal fistula. The patient was referred to our genetics unit for counseling at 33 years of age. A radiograph of the sacrum showed hemisacrum in both the patient and father, so familial CS was diagnosed. Patient MR showed an AM, without teratoma, whereas MR of the father was negative. The neurosurgeon suggested a conservative treatment (conservative management of the bowel) under clinical monitoring and to avoid pelvic trauma, the only possible risk in this case. If the patient had been a girl, treatment should have been surgical because of the risk of complications during pregnancy and delivery. Genetic analysis in the father and the child was negative for *HLXB9* mutations.



Fig 4. Pelvic MR of our case 5 shows a huge mass occupying the entire pelvis and compressing the spinal cord.

RESULTS AND DISCUSSION

CS has a variety of presentations, depending on the expressivity of the syndrome and on associated malformations. None of the 6 patients of our series (5 of them treated initially elsewhere) had an early diagnosis of CS despite the presence of ARM in all 6 and presacral mass in 5. Our series, although small, underlines that CS frequently is not recognized, and is misdiagnosed. This suggests, therefore, that it could be more frequent than currently estimated. CS can be diagnosed easily by a simple and low-cost radiograph of the sacrum showing the typical hemisacrum.

Our CS patients presented various associated anomalies not included in the classical description of CS. In particular, we observed 3 cases of dysganglionoses, 2 HD and 1 "not classifiable" dysganglionosis of the enteric nervous system (ENS). Constipation is commonly observed in CS, and it can be the first and only clinical

symptom. Some investigators¹⁷ ascribe it to a combination of anorectal maldevelopment, extrinsic compression, and neurologic factors. However, this hypothesis does not explain why constipation is frequently still present after surgery, and intestinal motility is affected much more frequently than bladder motility, as observed in the clinical practice. Our results about ENS anomalies of CS rectum could better explain the presence of constipation in these patients. Previous attempts to evaluate histology of the distal rectum in CS failed to find innervation anomalies^{18,19} but the techniques used to analyze rectal biopsies were not specified. To our knowledge, this is one of the first reports of dysganglionoses and HD associated with CS.²⁰ Taking into account the high percentage of ENS anomalies observed in our series (50%) and the possible embryogenetic relationships between rectal innervation and sacrum, we could consider dysganglionosis as a feature of CS rather than an associated anomaly. For this reason, the term of *Currarino syndrome* is more appropriate than *Curarrino triad*. CS patients presenting with constipation should be checked preoperatively for possible associated ENS anomalies. In 1999 Martucciello et al²¹ suggested to perform suction biopsies in ARM patients through the rectoperineal and rectovestibular fistula and to study them by AChE, lactate dehydrogenase (LDH), and NADPH-diaphorase (NADPH-d) enzymohistochemical techniques. In CS cases of preoperative diagnosis of ENS anomalies, it could be useful to resect the distal dysganglionic tract during anorectal surgery to improve PSARP functional results.

In 2 cases we also observed costal anomalies, characterized by costal fusions and accessory ribs. These malformations, never described until now in CS patients, were not clinically relevant. As frequently reported in the literature, we observed in our series urinary and gynecologic anomalies and neural tube defects (NTD). In particular, 3 cases of VUR (50%) were present, so we think that an evaluation of the urinary tract is essential in CS patients. Among NTD, tethered cord was present in a very high percentage of our patients (5 of 6, 83%) and lipoma in 2 (33%). Malignancy in CS has been reported in the literature in 4 cases, with an estimated frequency of 1%,¹² and included malignant teratoma in 3 patients²²⁻²⁴ and leiomyosarcoma in 1.²⁵ Our patient number 4 presented with an ectopic nephroblastoma. The possibility of malignant transformation should be considered, and a radical exeresis of teratoma or other neoplasias is a must of CS treatment.

Based on our experience, in which our series of patients did not benefit from a consistent and suitable diagnostic approach, we felt the need to establish an optimal diagnostic plan to avoid late diagnosis and ineffective treatment of CS. For this reason we propose a

combined diagnostic and therapeutic protocol for CS (Fig 5). A plain radiograph of the sacrum is the first diagnostic step, and it is indicated in every member of CS families, in suspected CRS, in every case of ARM, in children with unexplained severe constipation, and if a presacral mass has been diagnosed. Presacral mass as a first sign is rare in CS children and less rare in adults; the mass can be discovered accidentally or because of clinical problems. Sacrum x-ray should be performed in 2 projections (antero-posterior and lateral) in every case of ARM and CRS to calculate the sacral ratio.^{1,6} This latter is a valuable parameter for evaluation of sacral development in ARM patients, more accurate and easier than the number of sacral vertebrae, and it represents an important prognostic factor in ARM patients.^{1,6} However, for the diagnosis of CS, only the antero-posterior view is useful. The evidence of a hemisacrum is pathognomonic of CS. If a hemisacrum is present, molecular analysis of the *HLXB9* gene and radiologic study of the sacrum in parents and relatives is indicated to diagnose a sporadic versus familial CS. Parents and relatives with abnormal sacrum should be studied for *HLXB9* mutations. CS patients have to be studied for associated anomalies, as shown in Fig 5. Even if there are no descriptions of cardiac malformations associated with CS, cardiac evaluation has to be done in every patient because these malformations are commonly associated with CRS.

The urinary tract should be studied in every CS patient by US and, in case of radiologic or clinical suspicion of VUR, MCU should be performed.

In case of constipation (present in the majority of CS patients), a rectal suction biopsy is mandatory to rule out HD or other dysganglionoses. In our department, we perform rectal biopsy with the Solo-RBT instrument,²⁷ and we study ENS by AChE, LDH, and NADPH-d enzymo-histochemical techniques.

Even though presacral mass is well visualized by US, pelvic and spinal MR is mandatory in every patient and allowed us to classify CS into 3 different types: (1) Complete CS: CS with full expressivity, presenting with hemisacrum, ARM, and presacral mass. In that case diagnosis is possible at birth. (2) Mild CS: hemisacrum and only 1 of the other malformations, ie, ARM or presacral mass. In case of ARM, diagnosis is possible at birth, whereas in the other case, diagnosis is more difficult, presentation can be at later ages, and the main symptom is constipation. In this group, late diagnosis can sometimes cause many complications, morbidity, and mortality. (3) Minimal CS: only the hemisacrum is present. Even in this case constipation is frequent. Neural tube defects, particularly tethered cord, can be associated with CRS and also with CS, and spinal MR is the gold standard for evaluation of these anomalies, which can be associated with every type of CS.

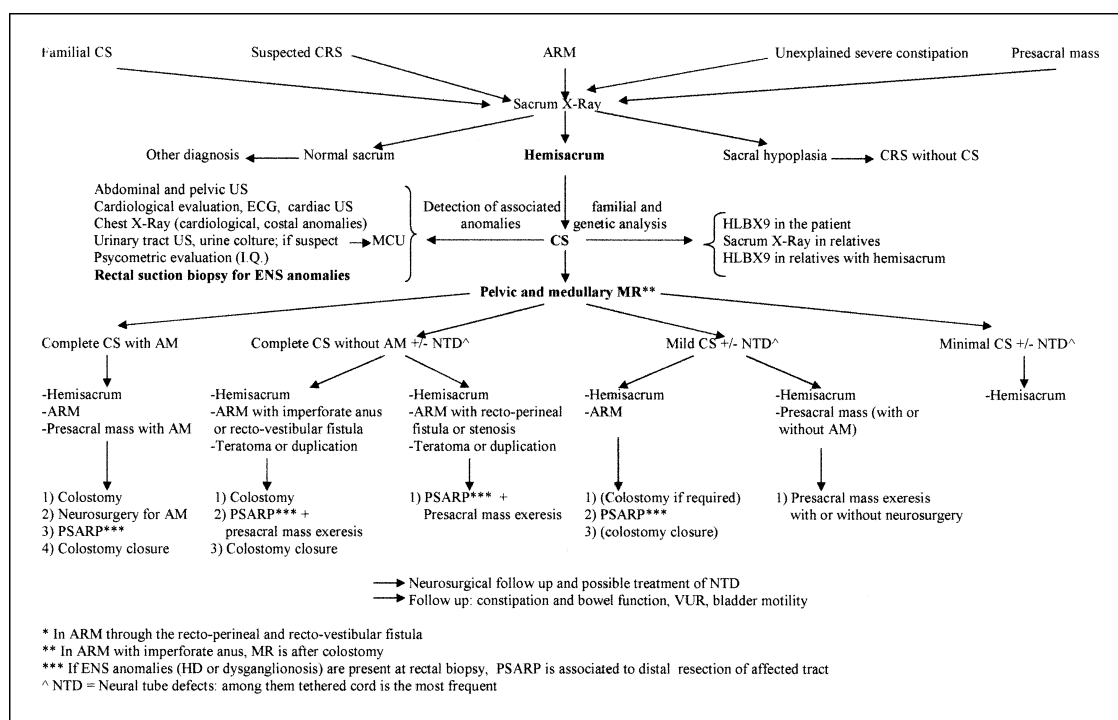


Fig 5. Proposal of a diagnostic and therapeutic protocol for CS.

Treatment differs according to CS type. In complete CS, we think that colostomy should be done before exeresis of the presacral mass. Neurosurgery is required if an AM is present. PSARP should be performed only at a subsequent stage.^{17,28} Colostomy closure is the last step. Some investigators suggest 1-stage treatment of AM and ARM after the colostomy^{19,29} but we think that this approach is hazardous for the risk of infections. In case of hemisacrum and ARM, primary PSARP can be performed, or, if ARM is high with imperforate anus or in some cases of rectovestibular fistula, previous colostomy is preferred, as in case of isolated ARM. If preoperative rectal biopsy is positive for HD or dysganglionosis, resection of the affected segment should be associated with PSARP. In case of hemisacrum and presacral mass, the exeresis of teratoma or other neoplasias should be done as soon as possible after diagnosis, even if asymptomatic, because of possible complications.²²⁻²⁵ If preoperative workup shows a cardiac anomaly requiring surgery, timing of surgery must be decided together with the heart surgeon. If VUR is present, the child should receive antibiotic prophylaxis. If surgical treatment of VUR is indicated, it should be performed last. In the follow-up, particular attention should be paid to bowel and bladder function, and constipation, if present, should be treated. The risk of CS transmission to the offspring is 50%, and to our knowledge, there is no correlation between the CS types in parents and children.

CS is a peculiar form of CRS, characterized by typical malformation of the sacrum (hemisacrum) and genetic etiology (mutations or deletions in the coding sequence of *HLXB9* gene). In addition to the main 3 features described by Currarino (hemisacrum, ARM, and presacral mass), other malformations can be found, like urinary, gynecologic, NTD, and costal anomalies. Particularly important for the final surgical results is the association with ENS anomalies like HD and other intestinal dysganglionoses, that could be considered as part of CS.

Because CS has been described no more than 20 years ago,⁵ this complex disorder is not universally known. Recent molecular genetics studies on this autosomal dominant disorder¹⁰ underlined the importance of this syndrome in pediatric surgery. The complexity and phenotype variability of CS requires a multidisciplinary approach. For a better coordination of the different diagnostic and therapeutic steps, we proposed a protocol that could represent a first attempt to optimize treatment and outcome of CS. A wider diffusion of the clinical and genetic aspects of CS could also reduce significantly its morbidity and mortality.

ACKNOWLEDGMENTS

The authors thank Anna Capurro for help in reviewing the manuscript.

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