Sacral agenesis

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Introduction

This article includes discussion of sacral agenesis, caudal dysplasia, caudal regression syndrome, Currarino syndrome, lumbosacral agenesis, sacrococcygeal agenesis, sacrum agenesis, syndrome of caudal regression, caudal regression, and hypoplasia of sacrum. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

The author reviews the clinical and pathological features of sacral agenesis, with emphasis on the resulting neurologic deficits and the association in many cases with maternal diabetes mellitus. The demonstrated wide spectrum genetic defects are reviewed in the context of molecular genetic regulation of ontogenesis of bony and neural spinal structures. Differential diagnosis from meningomyelocele, diastematomyelia, and congenital sacrococcygeal teratoma, an association with more extensive congenital anomalies, and management of the neurologic complications are discussed. The most serious complications are lack of bowel and bladder control due to anorectal atresia and flaccid neurogenic urinary bladder. The autosomal-dominant Currarino triad of sacral dysgenesis, anorectal malformations, and anterior meningocele is discussed, as well as caudal regression syndrome or syringomyelia.

Key points

- Agenesis of the sacrum and sometimes lumbar and even thoracic vertebrae is a congenital malformation that occurs sporadically, associated with other complex genetic syndromes and most frequently in infants of diabetic mothers (1% of all such infants). Rarely, it may be asymmetrical as hemi-sacral agenesis.
- Because of lack of neural tube (ie, floor plate) induction by the deficient notochord, at the level of the bony dysgenesis there is a severe dysplasia of the spinal cord, often with fusion of the ventral horns, an incomplete central canal, and abnormal architecture of white matter tracts.
- Clinical neurologic expression at birth is hypoplasia or aplasia of muscles innervated by the defective ventral roots, autonomic defects, and neurogenic bladder, but relative preservation of somatic sensory function of the dorsal roots.
- In its most extreme forms there may be a “caudal regression syndrome” of sirenomelia (fusion of the lower limbs), imperforate anus and other lower intestinal and urinary collecting system anomalies or the “Currarino triad” of anorectal malformation or ectopic anus, coccygeal and partial sacral aplasia, hypoplasia or dysplasia but preservation of the first sacral vertebra, and a presacral mass that often is an anterior meningocele, dermoid cyst, midline sacral lipoma, or a neuroendocrine tumor.
- The mechanism is abnormal segmentation of the embryonic sclerotomes with secondary failure of induction of the caudal neural tube and surrounding mesodermal structures.
- A strong association with maternal diabetes mellitus is of unknown pathogenesis, but suppressed genetic expression by insulin is suspected.

Historical note and terminology

Partial or complete absence of the sacral and coccygeal bones was first described in 1852 by Hohl (Hohl 1852); in 1857, Wertheim published a case of complete sacrococcygeal agenesis. Over the next hundred years, about 50 additional cases were published singly or in small series. In 1959, Blumel and colleagues reported 50 more cases, many of which included other malformations such as meningoceles, anal and bowel anomalies, and abnormalities of the lower limbs often associated with dysfunction of the bowel and urinary bladder. Sacral meningocele, often anterior, was noted by Coller and Jackson in 1943 to often be associated with sacral agenesis or sacral hypoplasia (Coller and Jackson 1943), and this association was subsequently confirmed by other authors. Case reports confirming the early descriptions continue to appear (Pouzet 1938; Williams and Nixon 1957; Smith 1959; Blumel et al 1962; Frantz and Aiken 1967; Ignelzi and Lehman 1974; Sarnat et al 1976). An association of sacral agenesis with congenital tumors in

the sacral region also is described, but this situation remains rare.

The frequent occurrence of sacral agenesis in infants of diabetic mothers was pointed out by Kucera in a survey that reviewed 48 papers published between 1930 and 1964 on the topic of congenital anomalies associated with maternal diabetes mellitus during gestation (Kucera 1971). The total incidence of all anomalies was 4.8%, and the incidence of sacral agenesis in infants of diabetic mothers is now estimated at about 1%, a more significant association than with any other predisposing condition, including genetic factors.

Caudal regression syndrome. The term "syndrome of caudal regression" was first used by Duhamel to describe a spectrum ranging from simple sacral agenesis to severe lower limb anomalies, including fusion as "sirenomelia," often with imperforate anus and major malformations of the anus and rectum, omphalocele, and anomalies of the genitourinary system, but sacrococcygeal agenesis or hypoplasia was the constant feature (Duhamel 1961; Boulas 2009). Rarely, there is duplication of the rectum rather than atresia or ectopia (Kratz et al 2008; Ozturk et al 2009). Children born with the syndrome or caudal regression also may lack pelvic bones and have agenesis of the fibulae and of the external genitalia, and they often live only a few hours (Akhtar et al 2005). Rare cases exhibit a vestigial tail despite sacral agenesis (Guven et al 2008), suggesting lack of induction at the sacral level and overinduction at the coccygeal level, in terms of pathogenesis. Many inconstant anomalies of multiple organ systems include single umbilical artery in one third of cases and congenital heart disease in more than half of cases as well as renal agenesis, genital anomalies, popliteal webbing, and cleft lip and palate (Al Kaissi et al 2008; Bruce et al 2009). Asymmetrical sacral agenesis associated with hemivertebrae occurs rarely (Gedikbasi et al 2009). The spinal cord may terminate at midthoracic levels, with a few bony vertebrae still developed caudal to that site (Bicakci et al 2014). Deficient sensory and motor innervation of muscle corresponding to the level of the dysplastic spinal cord may sometimes be improved in caudal regression syndrome by extended use of growth hormone combined with physiotherapy rehabilitation (Devesa et al 2017).

The clinical neurologic and neuropathologic findings in sacral agenesis were described by Sarnat and colleagues following fragmentary descriptions in the earlier literature and confirmed by subsequent observations (Sarnat et al 1976; Nagy et al 2009; Emami-Naeini et al 2010; Emami-Naeini et al 2012). Plain radiographic features had been described by many authors, and the MRI findings were systematically described by Nievelstein and colleagues (Nievelstein et al 1994). Radiographic and imaging findings of the bony spinal anomalies can be diagnosed at birth and prenatally as early as 26 weeks gestation (Boulas 2009; Gedikbasi et al 2009; Harris et al 2009; Nagy et al 2009). Though not generally familial, caudal regression syndrome has been found in 1 of dizygotic twins (Krenova et al 2010). Hemi-sacral agenesis occurs at times (Mesa 2011); in 1 case, it was discovered as an incidental finding in a (99m) Tc-MDP bone scan performed for other reasons in a 69-year-old woman (Karacalioglu et al 2008). In addition to imaging for the vertebral defects, presacral masses may be demonstrated in Currarino syndrome that are not necessarily evident on physical examination of the patient (Pérez Vega-Leal et al 2013).

Clinical manifestations

Presentation and course

Thin, flaccid lower limbs are evident in the neonatal period in cases of complete sacral agenesis or if the defect also involves lumbar segments, but minor defects of only the coccyx and lowest 1 or 2 sacral vertebrae may not show obvious clinical deficits at birth. Meningomyeloceles are usually small or occult, and are generally associated only with extensive defects. The meninges and nerve roots may herniate through the region of the defective vertebral centra and, thus, may extend anteriorly, rather than posteriorly, and not form an external cystic mass over the lower spine (Bryant 1938; Coller and Jackson 1943; Say et al 1977). Lipoma of the conus medullaris and filum terminale, fusion of nerve roots and ganglia, and aberrant sensory ganglia are additional defects in severe cases (Towfighi and Housman 1991). Palpation of the spinous processes of the newborn back may disclose a level below which only soft tissue is felt. About 17% have spina bifida bony deformities (Dounis 1978). The wings of the ilia may be rotated toward the posterior midline in the absence of an intervening sacrum. Half of the children have congenital subluxation or dislocation of 1 or both hips (Dounis 1978; Morimoto et al 2015).

The bony defect usually consists of total absence of the coccyx and of the lower 2 or 3 sacral vertebrae, hypoplasia of the 1 or 2 vertebral bodies immediately above the aplastic segments, and normally formed vertebrae at more rostral levels. Rarely, the sacral and lumbar articular facets are absent but the centrum or vertebral body is formed (Keim and Keagy 1967). In some cases the spinal bony defect may be extensive and involve the entire sacrum, lumbar, and even

thoracic vertebrae.

More severe and extensive vertebral defects may be accompanied by sirenomelia or fusion of the lower limbs in a "mermaid" configuration; this condition is nearly always associated with an ectopic or imperforate anus, malrotation of the bowel and sometimes omphalocele, genitourinary anomalies, and often hydronephrosis, rectovaginal fistula, and other visceral anomalies. The combination in sirenomelia is sometimes called the "syndrome of caudal regression" (Duhamel 1961; Passarge and Lenz 1966; Mar Molinero and Pascual-Castroviejo 1976; Welch and Aterman 1984; Guidera et al 1991; Towfighi and Housman 1991; Hudson and Ramsay 1993; McCoy et al 1994). Visceral anomalies of the gastrointestinal and genitourinary systems are not found exclusively with sirenomelia but also may accompany some cases of usually extensive vertebral defects without lower extremity fusion (Blumel et al 1962; Berdon et al 1966; Koontz and Prout 1968; Thompson et al 1974). Imperforate anus, anteriorized anus, and other anal anomalies occur in some cases (Capitanucci et al 1997). Aphallia was reported with urorectal septal anomalies and sacral agenesis in a male infant of a diabetic mother (Gripp et al 1999). Unilateral pulmonary atresia and tracheoesophageal fistula may occur rarely with total sacral agenesis (Bernbeck et al 2004).

All children with complete sacral agenesis have abnormal bladder and urethral function that not only causes incontinence but puts their kidneys at risk for progressive nephropathy; early detection is essential to prevent chronic hydronephrosis and indolent urinary tract infection (Wilmshurst et al 1999; Emami-Naeini et al 2012). Complete neurogenic bladder may occur with secondary renal impairment from hydronephrosis (Cho et al 2016). Anatomical anorectal malformations may cause rectovesical fistula and recurrent urinary tract infection (van der Steeg et al 2016). Pudendal neuromodulation is possible to monitor bladder and bowel dysfunction, and rectovesical fistula in particular, in sacral agenesis (Schober et al 2016).

Neurologic manifestations. The neurologic deficits in sacral agenesis are present at birth and involve motor functions more commonly than sensory functions, in a lumbosacral root distribution (Sarnat et al 1976). Autonomic involvement with a flaccid neurogenic bladder and hydronephrosis is variable and does not necessarily follow the extent of the somatic motor deficits (Sarnat et al 1976). Flaccid neurogenic bladder is a serious complication in many cases, and it is difficult to treat and to prevent hydronephrosis and recurrent lower urinary tract infections (Saito et al 1991; Unluer and Bult 1991). Exstrophy of the bladder is present in rare cases (Loder and Dayioglu 1990). Neurogenic bladder also may be associated with imperforate anus (Unluer and Bult 1991; Kakizaki et al 1994). Other gastrointestinal complications range from malrotations of the bowel and omphalocele to functional constipation probably due to poor peristalsis from defects in autonomic innervation of the gut (Hardwick et al 1992). Isolated neurenteric cysts in the lumbar region are reported in sacral agenesis (Mendel et al 1994). A rare clinical presentation in the neonate is abdominal distension in an infant at risk for necrotizing enterocolitis (Oei and Koh 1998).

Marked sensory deficits usually indicate an occult meningomyelocele that may be accompanied by a Chiari malformation and hydrocephalus. Spinal dorsal root ganglia and the dorsal horns of the spinal cord are usually preserved in sacral agenesis (Sarnat et al 1976) but occasionally may be defective or absent even without open neural tube defects (Towfighi and Housman 1991). Impaired parasympathetic and somatic motor innervation of the lower rectum and anal sphincter may be present (Morera and Nurko 2003).

The motor deficits are due in part to nerve root hypoplasia or dysplasia with lack of complete innervation of fetal muscle, in part to dysgenesis of the spinal cord and a deficient number of motor neurons, and in part to primary amyoplasia. At times, the dermis also is hypoplastic and only adipose tissue with a few small wandering nerves is interposed between the usually (except in sirenomelia) normally formed long bones and the epidermis. More extensive neuropathies accompany more extensive vertebral defects to higher levels of the spine, and extension into the thoracic spine may be associated with diaphragmatic hernias and respiratory distress at birth. The neurologic deficits are generally symmetrical. Rarely, incomplete sacral agenesis may be associated with terminal lipomyelocystocele (Ramdurg et al 2013).

The spinal cord may be tethered in sacral agenesis (Emami-Naeini et al 2010), and syringohydromyelia or syringomyelia may be present as demonstrated by MRI (Nievelstein et al 1994; O'Neill et al 1994). Because of the tethered spinal cord, the neurologic deficits may be slowly progressive as the child grows (Emami-Naeini et al 2010; Emami-Naeini et al 2012). Particularly in Currarino syndrome, presacrococcygeal mass lesions may occur with malignant neuroendocrine transformation (Ciotti et al 2011).

Orthopedists classify distal spinal agenesis into categories (Renshaw sacral agenesis types 1 to 4) that correlate with

ambulatory and other motor functional abilities (Van Buskirk and Ritterbusch 1997). Acetabular dysplasia of the hip may accompany unilateral or bilateral sacral agenesis (Morimoto et al 2015). Rib grafts can be used to promote spinopelvic fixation in some patients with sacral agenesis (Ferland et al 2015).

Rarely, malformations of left-right asymmetry of visceral organs, including anomalous superior and inferior vena cavae, are present in infants with sacral agenesis who are born to diabetic mothers (Lin et al 1998).

Prognosis and complications

The prognosis for neurologic improvement is poor. Survival and quality of life depends largely on the management of the major visceral complications, such as hydronephrosis and anomalies of the gastrointestinal tract and anus. Occult meningomyeloceles should be demonstrated and treated as indicated. They may be accompanied by Chiari malformation and hydrocephalus. A longitudinal study of bowel function in children with sacral agenesis showed successive spontaneous improvement with age, though the children did not achieve normal bowel control (Borg et al 2013). Fecal incontinence is a difficult complication of sacral agenesis (Macedo et al 2004; Thomas et al 2013).

Biological basis

Etiology and pathogenesis

The most common predisposing factor in the etiology of sacral agenesis is not chromosomal, but rather maternal diabetes mellitus. The majority of infants with sacral agenesis have diabetic mothers, and approximately 1% of all infants born to diabetic mothers have agenesis of at least the coccyx and the lower 1 or 2 sacral vertebrae (Rusnak and Driscoll 1965; Passarge and Lenz 1966; Szalay 1975; Cousins 1983; Horton and Sadler 1983; Kalter 1993; Gripp et al 1999). Sacral agenesis should be regarded as a part of a spectrum in the programming of the entire caudal region of the embryo, rather than as an isolated anomaly (Catala 2002). Partial sacral agenesis associated with a dorsal enteric sinus and spina bifida is attributed to “split notochord syndrome” (Nanda et al 2010) but really is more likely a form of neurenteric cyst. Rarely, rather than just dysplastic spinal cord at the level of the bony hypoplasia of lumbar and sacral vertebrae, there may be absence of a segment of spinal cord altogether, but with preservation of the conus medullaris, the most caudal portion that forms by secondary, rather than primary, neurulation, termed “junctional neural tube defect” (Schmidt et al 2017).

No constant genetic or chromosomal disorders are associated with sacral agenesis, but isolated cases are described. Some anterior spinal defects appear to be inherited as an autosomal dominant trait (Yates et al 1983). A gene for autosomal dominant sacral agenesis maps to the holoprosencephaly region at 7q36 (Lynch et al 1995), though holoprosencephaly is not usually complicated by sacral agenesis. Mutation in the HLXB9 transcription factor also causes an autosomal dominant form of sacral agenesis (Catala 2002). Furthermore, in 5 families with mirror polydactyly and sacral agenesis, no mutations were demonstrated (Vargas et al 1998). This gene is the primary genetic defect in Currarino syndrome as a specific form of sacral agenesis, but it is not involved in the pathogenesis of the caudal regression syndrome (Merello et al 2006). Several cases of sacral agenesis are reported with terminal deletion of the long arm of chromosome 7, with 7q35 and 7q36 deletions in particular appearing as an important genetic etiology (Ayub et al 2016). A locus for sacral agenesis with anorectal malformations has been mapped to 6q25.3 in a 0.3 Mb interval region (Titomanlio et al 2006). A whole exome sequencing and copy number pilot study concluded that despite great genetic diversity and complexity of the phenotype, common genetic features would be identified in patients with sacral agenesis (Porsch et al 2016).

There is no significant gender difference (Dounis 1978). In some cases, the occurrence of sacral agenesis in siblings suggests an autosomal recessive trait (Muthukumar et al 1992; Sarica et al 1998), but autosomal dominant inheritance without expression in a parent is possible. X-linked dominant inheritance of partial absence of the coccyx and sacrum also is described rarely in other families (Cohn and Bay-Nielsen 1969). An infant with a 7q36-->7qter terminal deletion had sacral agenesis and also holoprosencephaly (Morichon-Delvallez et al 1993), but midline cerebral malformations are not generally associated with defects of the lower spine. Another fetus also is reported with 7q36.1-->qter monosomy and sacral agenesis with severe intrauterine growth retardation, but this fetus did not have holoprosencephaly (Savage et al 1997). Structural rearrangements of the long arm of chromosome 7 with terminal deletions of chromosome 7 (q36-qtr) (Wang et al 1999; Su et al 2008), ring chromosome 7 (Rodriguez et al 2000), or deletions at band 7q36 (including the Sonic hedgehog gene), or 7q36-qter terminal deletion in infants with sacral agenesis and anterior myelomeningocele, are demonstrated (Vance et al 1998; Rodriguez et al 2002). Combination

duplication/deletion of distal 7q also is demonstrated in some children with the Currarino triad (Pavone et al 2010).

Missense mutation of the human T-gene (*brachyury*), a transcription factor essential for the normal development of posterior mesodermal structures and defective in vertebral malformations, is suggested as a possible cause of sacral agenesis (Ghebranious et al 2008). A murine form of T-gene mutation is known, but this gene is not confirmed as an etiology of sacral agenesis in the mouse (Papapetrou et al 1999).

Currarino triad. A specific type of sacral agenesis of autosomal dominant transmission is identified as "Currarino triad or syndrome." It consists of a unique complex of congenital caudal anomalies that include (1) anorectal malformation or ectopic anus, (2) coccygeal and partial sacral aplasia, hypoplasia, or dysplasia, and (3) a presacral mass that often is an anterior meningocele, dermoid cyst or lipoma (Lynch et al 2000; Kochling et al 2001; Kurosaki et al 2001; Le Caignec et al 2003; Bunc et al 2009; Pavone et al 2010). The spinal cord may be tethered, and the brain may be micrencephalic but with a normal convolutional pattern (Pavone et al 2010). Anorectal stenosis may be present, and bacterial meningitis may result from neurenteric fistulas with the spinal canal (Tamayo et al 1999). A presacral mass may be present in some cases, and Hirschsprung disease may also occur (Kilickesmez et al 2006). Neonatal lumbar teratoma is reported (Guvenc et al 2006). Higher anomalies in the GI tract, such as esophageal stenosis or atresia, are also described (Akhtar et al 2005). Though generally diagnosed in the neonatal period, infancy, or early childhood, the diagnosis of the Currarino triad sometimes is not established until adult life (Berghauser et al 2012).

Constipation is the most frequent presenting clinical symptom of the Currarino triad (Calleja Aguayo et al 2012). Presacral lipomeningocele and teratoma may be present. The most common anorectal malformation is the anal stricture, which may be associated with fecal incontinence; recurrent meningitis may result from unrecognized recto-meningeal fistulas, and the mortality rate of 56% is high (Calleja Aguayo et al 2012).

Mutations or microdeletions are demonstrated in the homeobox gene *MNX1* (formerly *HLXB9*) that encodes the nuclear protein HB9; these genetic alterations are found in the majority of, but not all, patients with the Currarino syndrome phenotype and various novel mutations are demonstrated (Ross et al 1998; Hagan et al 2000; Kochling et al 2001; Merello et al 2006; Garcia-Barcelo et al 2009; Zu et al 2011; Merello et al 2013). A de novo 7q36.1-qter deletion is reported in Currarino syndrome with sacral agenesis and without structural malformations of the brain (Horn et al 2004), but de novo nonsense and frameshift mutations also are described, generally in association with presacral tumors (Zu et al 2011). In other cases a distal 7q chromosomal imbalance may involve micrencephaly with intellectual disability, sensorineural deafness, and somatomedin C deficiency (Pavone et al 2010). Another locus at 6q25.3 is demonstrated in sacral agenesis with anorectal malformations (Titomanlio et al 2006). A murine model of genetic knockout of this gene is described, and the affected mice also have sacral agenesis and visceral anomalies, including agenesis of the dorsal pancreas (Li et al 1999).

Sacral agenesis also has been reported rarely with presacral and intraspinal tumors, particularly extradural lipomas, dermoids, and sacrococcygeal teratomas (Kenefick 1973; Hafeez and Tihansky 1984; Jindal and Mahapatra 2000; Santi et al 2008; Shanske et al 2008), but some of the benign tumors are part of the Currarino triad as described above.

All primary and associated defects in sacral agenesis can be dated to before the seventh gestational week (Mills et al 1979). The basic defect occurs during the formation of somites, probably due to a mutation of an early regulatory homeobox gene, and is followed by defective induction of the somite and of the neural tube.

Cnot is a homeobox gene expressed early by cells of Henson node and the notochord, but also by the postnodal neural plate caudal to the future hindbrain (Stein and Kessel 1995). If this gene is defective, the notochord does not form normally. Pax-1 is another homeobox gene that is expressed in sclerotome cells, but only in the presence of an intact notochord (Koseki et al 1993). It is a mediator of notochordal signals for the dorsoventral specification of sclerotomes that will form the ventral parts of vertebrae. The ventralizing gradient effect of the notochord on the somite is mediated by an inductive gene: Sonic hedgehog (Fan and Tessier-Lavigne 1994). Mutant genes or deletions of nucleotide sequences are not proved in sacral agenesis, hence, defective regulator genes are still hypothetical, but these are examples of genes that, if incompletely expressed, could potentially explain the failure of the sclerotome and perhaps also of the myotome and dermatome of the somite to form over a restricted number of segments. A mutation in the T (*brachyury*) gene produced a syndrome of sacral agenesis and persistent embryonic notochordal canal in 3 consanguineous families (Postma et al 2014). Somitogenesis and vertebral development require several growth factors and enzymes in the extracellular matrix, without which sacral agenesis or more extensive lesions of the

vertebral column may appear (Achilleos et al 2015). A rare spinal dysraphism, myelocystocele, may result in a split and tethered spinal cord, syringomyelia, and sacral agenesis (Bansal and Mahapatra 2015; Mankotia et al 2015).

The failure of the notochord to form properly in the lumbosacral region results in deficient induction of both the floor plate of the overlying neural plate and of the somites, particularly the ventral part of the somite that contains the sclerotome (Sarnat 1992; Pourquie et al 1993). The myelodysplasia involves mainly the ventral half of the neural tube; the ventral horns and roots are defectively formed or incomplete, and the central canal is dysplastic (Sarnat 1992; Hudson and Ramsay 1993). The neural crest tissue that separates from the dorsal midline at the time of neural tube closure is not primarily involved; hence, the sensory function is preserved. However, autonomic axons of dorsal and ventral roots may be defective, in part secondary to involvement of the intermediolateral columns of the spinal cord where the preganglionic neurons may be deficient.

Sacral agenesis may be experimentally induced in chickens by the injection of insulin into incubating eggs in early gestation (Landauer 1945; Duraiswami 1950), and sacral agenesis also occurs in the pups of diabetic rats but may be prevented by insulin therapy (Eriksson et al 1982). Insulin in certain concentrations might interfere with the differentiation of the caudal chorda-mesoderm, but fetal insulin secretion does not begin until after the critical period of teratogenesis and maternal insulin does not enter the placental circulation (Adam et al 1969; Kalhan et al 1975; Mills et al 1979). On the other hand, structurally unique insulin receptors are found on cerebral neurons, but not other cells in the brain, and these receptors play a role in neuronal growth and differentiation that is unrelated to glucose homeostasis (Heidenreich 1991). Rarely, human patients with adrenal and growth hormone insufficiency are associated with sacral agenesis (Gundgurthi et al 2011). Sacral agenesis occurs on a genetic basis in a strain of mice (Frye et al 1964) and may be induced in rodents by streptonigrin and certain other teratogens (Warkany and Takacs 1965).

Multiple additional spinal anomalies may accompany sacral agenesis (Özmen et al 2016). Some, such as kyphosis and scoliosis, may develop secondarily during infancy or childhood (Balioglu et al 2016). Lack of a sacrum is reported in the fetal amniotic band syndrome with umbilical cord entrapment diagnosed by antenatal ultrasound studies at midgestation (Gupta et al 2015), but the role of amniotic bands early in gestation when sacral agenesis develops is uncertain.

Epidemiology"

Maternal diabetes mellitus is the most important predisposing factor. Both genders and all ethnic groups are affected.

Toxin- or drug-induction of sacral agenesis in early gestation may be an etiology in rare cases: 1 infant is reported with severe aplasia of the entire lower body pole and visceral anomalies, putatively related to the maternal use of minoxidil to prevent hair loss, prior to and during gestation (Rojansky et al 2002).

Prevention

Good control of blood sugar in early gestation in diabetic women may minimize the risk, but this is not proved. Prenatal diagnosis by ultrasound studies before mid-gestation is possible in some cases (Sonek et al 1990).

Differential diagnosis

The major differential diagnosis is spina bifida and other defects of the lower spine, such as diastematomyelia, that are associated with neural tube defects. Rare congenital tumors of the sacral or presacral region, particularly teratomas, also should be considered. Ultrasound often is able to detect sacral agenesis in utero (Radulescu et al 2012). Prenatal genetic studies may be helpful if a sacral lesion is discovered by ultrasound (Le Caignec et al 2003).

Diagnostic workup

Plain roentgenograms of the lower spine reveal the bony defect, though ossification of the neural arches is incomplete at birth. MR imaging of the sacral region not only provides more detail but also discloses occult meningomyeloceles, lipomas, lipomeningoceles, and neurenteric cysts, and may demonstrate the small size and aberrant course of nerve roots (Mendel et al 1994; Nievelstein et al 1994; O'Neill et al 1995; Capitanucci et al 1997). An abnormal bulbous or club-shape of the conus medullaris may be demonstrated by MRI, as well as tethering of the spinal cord (Jagtap et al 2013; Boruah et al 2016). An abnormal conus medullaris can also be demonstrated prenatally by fetal sonography and

MRI (Mottet et al 2016). Anterior Anterior sacral meningoceles may be asymptomatic but diagnosed by MRI (Beyazal 2013). CT imaging provides less detail of the type needed. Associated anomalies of the gastrointestinal and genitourinary systems also may be seen by MRI. Additional radiological studies of the visceral anomalies may be helpful in such cases. Imaging of the brain may be indicated to reveal malformations of the forebrain or of the posterior fossa associated with maternal diabetes mellitus. Roentgenograms and CT of the thorax may demonstrate unilateral or bilateral pulmonary atresia in a minority of cases of total sacral agenesis (Bernbeck et al 2004). Closed neural tube defects in children with caudal regression syndrome may be detected by various modalities of imaging (Jeelani et al 2013). Prenatal diagnosis by fetal imaging of caudal regression syndrome is now possible (Beaumont et al 2013).

The EMG reveals neuropathic changes in the external sphincters of the bladder and anus. Denervation of muscles of the pelvic floor correlates poorly with the level of the sacral bony defect. No EMG activity is detected in the legs of patients with complete sacral agenesis (Boyd 1989), probably because of amyoplasia or end-stage fetal neurogenic atrophy. Postoperative EMG including perineal-evoked potentials may be useful following surgical repair of spinal dysraphism including some cases of sacral agenesis, particularly for urodynamic assessment in patients at risk of neurogenic bladder (Torre et al 2002). Muscle biopsy is rarely indicated.

Urinary tract studies, including renal ultrasound, voiding cystography, renal nuclear scan, and urodynamic studies, are essential because irreversible damage may be prevented and function improved (Boemers et al 1996; Capitanucci et al 1997; Emami-Naeini et al 2010; Emami-Naeini et al 2012). Recurrent urinary tract infections may present in children with urological complications of sacral agenesis (Emami-Naeini et al 2012). In the neonate, anal patency should be determined soon after birth. Rectal manometry in patients with sacral agenesis may be useful in quantitating changes in anorectal function association with impaired parasympathetic innervation and in analyzing fecal incontinence in older children (Morera and Nurko 2003). All infants and children with sacral agenesis, lower spinal cord anomalies, and Currarino triad should have urinary bladder and anorectal functions investigated early because of the high incidence of impairment that can lead to chronic complications (Borg et al 2009). Bowel dysfunction in infancy improves spontaneously in most children with sacral malformations (Borg et al 2013).

Though rare, hypopituitarism is reported in sacral agenesis, so that an endocrinological workup may be indicated (Gundgurthi et al 2011).

Genetic studies of chromosomal defects or specific genetic mutations may be helpful in some cases, even prenatally: haploinsufficiency of HLXB9 by FISH analysis is associated with the triad of presacral mass (teratoma or anterior meningocele), sacral agenesis, and anorectal malformation - the defining features of the Currarino syndrome (Le Caignec et al 2003; Horn et al 2004). Mutation analysis and genetic counseling are essential, particularly in Currarino syndrome (Ciotti et al 2011; Zu et al 2011). A homozygous mutation in the T (*brachyury*) gene causes sacral agenesis but also preservation of the notochord and typical neurologic deficits of caudal regression syndrome in the lower extremities, diagnosed prenatally by sonography (Fontanella et al 2016).

Management

Visceral anomalies such as malrotation of bowel, omphalocele, imperforate anus, or meningomyelocele not covered by skin all require surgery in the first 24 hours after birth. Hydronephrosis and (rarely) hydrocephalus may require urgent attention within the first week. If the infant is born to a diabetic mother, neonatal hypoglycemia is a common complication that must be watched vigilantly. Chronic nephropathy secondary to anomalies of the lower urinary tract is important to recognize early and treat (Wilmshurst et al 1999). The urological outcome of patients with sacral agenesis may be good if neurogenic bladder is recognized early, but many patients are not diagnosed until late childhood when they present with urinary incontinence; all require lifelong surveillance (Abascal Junquera et al 2006; Emami-Naeini et al 2012).

Reconstructive procedures to compensate for the bony defects, separate fused lower limbs, create a new anal opening, or revise the genitalia are done electively after the neonatal period (O'Neill et al 1995). In asymmetrical or hemi-sacral agenesis, transiliac lengthening with posterior lumbar-iliac percutaneous fusion may be successful (Mesa 2011). The neurologic deficits and amyoplasia cannot be improved by surgery. Neurogenic bladder is 1 of the most frequent complications requiring continuous urological care and may be accompanied in some cases by bilateral vesiculo-ureteral reflux (Boemers et al 1996a; Boemers et al 1996b; Capitanucci et al 1997). Early diagnosis, including urodynamic studies, and treatment may prevent irreversible damage to the urinary tract and kidneys and may achieve

urinary continence if partial function is preserved. In addition to surgery of the urinary tract, urinary continence may be restored in some cases by surgical correction of intraspinal lesions such as lipomeningocele, dorsal lipoma, and tethered spinal cord (Muthukumar 1996). The release of tethered spinal cord also prevents the progression of other neurologic deficits (O'Neill et al 1995). Associated hydromyelia and syringomyelia do not generally require surgical intervention (O'Neill et al 1994; O'Neill et al 1995). The resection of dorsal hemivertebrae associated with sacral agenesis prevents progressive spastic paraplegia of residual motor function in the lower extremities (Zidorn et al 1994). Sacral hemi-agenesis has been found as an incidental finding in bone scans as well (Karacalioglu et al 2008).

Imperforate anus and other anal anomalies should be diagnosed at birth and may require early treatment (Boemers et al 1996). Fecal incontinence may be an issue in older children (Morera and Nurko 2003). In studying children with fecal incontinence and anorectal malformations, the “sacral ratio,” calculated from anteroposterior and lateral roentgenograms, does not correlate and, hence, is not predictive in infancy for identifying children who will later have fecal incontinence (Macedo et al 2004). Pelvic widening may alleviate the mechanical component of constipation in caudal regression syndrome in children with an extremely narrow pelvis (Sathya et al 2013). Laparoscopic diversion into augmentation cystoplasty was performed in a child with sacral agenesis (Ramalingam et al 2013). Electrical stimulation of the sacral nerve by an implanted pulse generator may be useful in fecal incontinence as a complication of sacral agenesis (Thomas et al 2013; Brunner et al 2016). Pudendal or sacral “neuromodulation” in sacral agenesis may be beneficial for bowel and bladder dysfunction (Schrober et al 2016; Lagares-Tena et al 2017).

Tethering of the caudal spinal cord must be treated surgically, as early as possible, to treat and avoid further progressive neurologic deficits (O'Neill et al 1995; Emami-Naeini et al 2010). The results of surgery in Currarino triad can be rewarding (Isik et al 2010). Junctional neural tube defects with segmental absence of spinal cord do not exhibit tethering (Schmidt et al 2017).

In caudal regression syndrome, chronic administration of growth hormone with rehabilitative measures may improve distal innervation over time (Devesa et al 2017).

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**References especially recommended by the author or editor for general reading.

ICD and OMIM codes

ICD codes

ICD-9:
Sacrum agenesis: 756.13

ICD-10:
Other congenital malformations of spine, not associated with scoliosis: Q76.4

OMIM numbers

Currarino syndrome: #176450

Profile

Age range of presentation

0-01 month
1 month to adolescence

Sex preponderance

male=female

Family history

none

Heredity

heredity may be a factor
autosomal dominant
autosomal recessive
X-linked recessive

Population groups selectively affected

none selectively affected

Occupation groups selectively affected

none selectively affected

Differential diagnosis list

spina bifida
other defects of the lower spine
diastematomyelia
rare congenital tumors of the sacral or presacral region
teratomas

Associated disorders

Anorectal malformations
Anterior meningocele
Hirschsprung disease
Maternal diabetes mellitus
Meningomyelocele
Recto-meningeal fistula
Sacral teratoma

Other topics to consider

Hypoglycemia
Intellectual disability
Klippel-Feil syndrome
Meningomyelocele
Neurogenic bladder

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