Skip segment Hirschsprung’s disease in a patient with Shah-Waardenburg Syndrome

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A B S T R A C T

Introduction: We present a new case of Skip segment Hirschsprung’s disease (SSHD) associated to Waardenburg’s syndrome, in a patient with total colonic aganglionosis (TCA). Even though there are more than 30 cases reported in the literature, SSHD’s existence is controversial, due to the fact that there is not clear embriological theory to explain this phenomenon.

Case report: 20 months-old male patient, that at four days-old had a temporary ileostomy because of an episode of intestinal obstruction. A microileum and right microcolon was observed at the moment of surgery. Biopsies of the ileum and microcolon confirmed the aganglionism. At four months-old definitive surgery was performed according to Boley’s procedure. Hystopathological study of the surgical piece showed absence of ganglion cells in cecum and ascending colon (SSHD). The postoperative has been favorable. A mutation in SOX10 gen was objectified in the molecular study, that confirmed the Shah Waardenburg syndrome.

Discussion: Most of cases of SSHD were observed in patients with TCA, as in our case. These patients usually need a temporary stoma before the definitive surgery. We think that the only way to discover SSHD cases is to make extended biopsies in left, transverse and right colon, and in ileum, while performing the ileostomy or in the definitive surgery.

Conclusion: SSHD must be included as a new phenotype in Hirschsprung spectrum. Preservation of these intestinal segments can improve intestinal function, specially in patients with TCA.

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Hirschsprung’s disease (HD) is characterized by the absence of the enteric nervous system in the bowel [1]. In most cases, the disease involves the rectum or rectosigmoid, but it can involve (5—10% of the cases) the entire colon or even a significant amount of the small intestine [1]. HD results from failure of enteric neural crest-derived cells to complete colonization of the intestine during fetal development (5th to 12th weeks of gestation) [2,3]. It is postulated that the earlier arrest of migration, the longer the resulting aganglionic segment [3]. Skip segment Hirschsprung’s disease (SSHD) is a rare phenomenon, involving a ‘skip area’ in a normally ganglionated intestine, which is surrounded proximally and distally by aganglionosis [3]. The occurrence of SSHD has no clear embryological explanation and its diagnosis may be missed as it is rarely suspected at initial surgery. Despite the first case being reported as early as 1954 [4] and the 30 cases that have been reported to date, its existence is often questioned on theoretical grounds. Waardenburg syndrome (WS) is a rare autosomal recessive neurocristopathy with variable presentation. Four types of WS are described. Type-IV is the association of WS with HD. This type is called Shah-Waardenburg Syndrome (SWS). The classic presentations of SWS include HD, sensorineural deafness, and depigmentation of hairs, skin, and the iris [5]. In patients with SWS, the aganglionic segment may be long and may have total colonic or total intestinal aganglionosis [6,7]. The treatment of HD is surgical and involves the removal of the aganglionic segment and anastomosis of the innervated bowel to the anus above the dentate line [1].

The aim of this report is to present a new case of SSHD in a patient with total colonic aganglionosis associated with Waardenburg syndrome and a systematic review of literature.

1. Case report

A 20-month-old male child is the first child of non-consanguineous healthy parents, born at term with a birth weight of...
2550 g. Family history (second degree) of HD was present. There was history of failure of meconium passage within the first 48 hours. Twelve hours later, the patient began to display feeding intolerance, abdominal distention and bilious vomiting. On admission he was noted to be in poor general condition with signs of dehydration and jaundice, while also displaying painful abdominal distention. There was no explosive stool after digital rectal exam, but narrow rectal ampulla was observed. The patient had blonde hair and blue eyes, with rotatory nystagmus. A plain abdominal X-ray (Fig. 1) showed dilated loops (probably of the small intestine), and no gas was observed in the distal colon, suggesting intestinal obstruction. A left microcolon was identified through an enema study with gastrografin. The laparatomy performed at four days old identified a microcolon and microileon (80 cm), with proximal dilatation; therefore, a temporary ileostomy was made. Also, intestinal biopsies (microileum and microcolon) were performed, which confirmed the aganglionism.

The patient remained hospitalized for a few months due to several episodes of enterocolitis, and as result of the malabsortion related to short bowel syndrome. A contrast enema (Fig. 2) made in the fourth month revealed a left microcolon and normal appearance of the right colon.

Afterward, a Boley type ileocoloplasty (Fig. 3), with mechanical suture, was performed. In it, a segment (10 cm) of the right colon was anastomosed to a normal ileon. Next, the cecum, with a part of the ascending colon, left microcolon and microileon were resected (Fig. 4). The intervention was completed by ileorectal anastomosis (Rehbein procedure). The patient had a favorable evolution during the postoperative period, needing daily rectal irrigations with saline, in the first months of his life. Nowadays the patient has good weight for height development. A hystopathological study of the resected intestine (Fig. 4) revealed the presence of ganglion cells in a 10 cm segment of the right colon (cecum and ascending colon) and aganglionism in the rectum, rectosigmoid, descending colon and microileum (Fig. 5A–D) (skip segment Hirschprung’s disease). Stunted psychomotor development was observed, associated with deep bilateral deafness. Carotid type and metabolic studies came back normal. Aberrant myelination was found through magnetic resonance imaging. A molecular genetic study showed a novo mutation in SOX10 gene that confirmed the SWS syndrome.
2. Discussion

Skip segment Hirschsprung’s disease (SSHD) is a term used to refer a normally ganglionated intestine, surrounded proximally and distally by aganglionicosis. It cannot be confused with ‘zonal aganglionicosis’, that refers to an aganglionic intestinal segment between two normally innervated segments [8]. ‘Double zonal aganglionicosis’ refers to an aganglionic segment that contains an area of normal innervation; it differs from SSHD in that, in the later, the rectum is always aganglionic whereas in ‘double zonal’ aganglionicosis, it can be ganglionic [9]. HD is the most common neurocristopathy in humans (1/5000 new borns) and is characterized by the absence of ganglion cells along an intestinal segment that in 70–80% is the distal segment, i.e. the rectosigmoid [2]. This condition causes the affected segment to disfunction and episodes of intestinal obstruction, especially in newborns [10]. The lower limit of HD is always constant (internal anal sphincter) while the upper limit is variable. This allows us to classify HD into various phenotypes: Short segment (S-HD: aganglionosis up to the upper sigmoid colon), long segment (L-HD: aganglionosis up to the splenic flexure and beyond), and the total colonic aganglionosis (TCA) forms [11].

According to our review of the English literature (Table 1), there are more than 30 described cases of SSHD [3,9,12–17] therefore, this phenotype should be included in the HD spectrum. Of all those cases, approximately 90% were observed in the TCA with the remaining cases being the rectosigmoid type of HD. The length of the SSHD segment, according to the cases described, has oscillated from a few centimeters (9 cm) in some children, to the entire ganglionated transverse colon in others [3,12]. The SSHD in our patient, according to the hystopathological study, affected the cecum and ascending colon (10 cm). HD’s etiology has no clear explanation, but the participation of the main genes (RET, EDNRB, EDN3, SOX10) is known; they are responsible for the migration, proliferation, differentiation and survival of the neural crest-derived cells during the embryonic enteric nervous system (ENS) development (5th to 12th weeks).

Fig. 4. Surgical piece: Left microcolon and 80 cm of microileum. Normal appearing of the right colon. A 10 cm segment of ascending colon and initial segment of transverse colon (used in the ileocoloplasty) is not shown.

of gestation) [18]. The consequence of these genes mutations is the absence of the enteric nervous system (ENS), that is, aganglionosis in an intestinal segment. However, the occurrence of SSHD currently has no clear embryological explanation. The most convincing theory, according to studies in murine mice, is that SSHD comes from an anormal pattern of extramural migration of the neural crest cells, during embryological development [14]. In 70% of HD’s cases the condition appears clinically isolated, with the remaining cases being associated with other neurocristopathies, like Waardenburg syndrome (1/50,000 newborns), chromosomopathies (Down syndrome in 1/750 newborns), and other congenital diseases (18% of patients). In our case, as in the one described by Gross et al. [14], SSHD is associated with Waardenburg syndrome, confirmed in both cases by molecular study [19]. A family history of HD can exist (our patient had a second degree family member). The heredity can be dominant or recessive, with reduced penetrance, and is mostly found in males. The risk of recurrence between brothers is 200 times more than in the general population [11].

A rectal suction biopsy, showing aganglionosis in the submucosa, is the golden standard for HD’s diagnosis [20] and a contrast enema is useful to gauge the transitional segment and know the extension of the aganglionism, but neither allow for detection of SSHD.

Most patients with TCA need a temporary ileostomy before definitive surgery. That’s why we agree with Burjonrappa and Rankin [15] that, apart from searching for more than one transitional segment, extended segment intestinal biopsies in the left and the right colon, the cecum and the small intestine should be included in the diagnosis of SSHD in L-HD and TCA. If we had proceeded like this, we probably would have changed the surgical technique, using Kimura’s procedure, as Raguhnath et al. describe [9]. The small intestinal segment in our case was quite long (80 cm), which could have avoided the resection of the right colon. Although Boley’s procedure (Fig. 4) had a favorable functional result, the patient needed daily rectal irrigations with saline during the first postoperative months in order to prevent enterocolitis.

### 3. Conclusions

To conclude, SSHD has enough identifying features to be included in the HD’s classification as a new phenotype. In patients with TCA we should investigate the possibility of SSHD, because preservation of these segments can have a positive influence on the postoperative functional results.

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**Table 1**

Cases of SSHD reported in the literature from 1954 to 2016.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Sex</th>
<th>Number of patients</th>
<th>Location of skip segment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keefer</td>
<td>1954</td>
<td>M</td>
<td>1</td>
<td>Rectosigmoid with skip in sigmoid colon</td>
</tr>
<tr>
<td>Sprinz</td>
<td>1961</td>
<td>F</td>
<td>1</td>
<td>TCA except skip in transverse colon</td>
</tr>
<tr>
<td>MacIver</td>
<td>1972</td>
<td>M</td>
<td>1</td>
<td>Rectosigmoid with skip in sigmoid colon</td>
</tr>
<tr>
<td>Martin</td>
<td>1979</td>
<td>M</td>
<td>1</td>
<td>TCA except skip in transverse colon</td>
</tr>
<tr>
<td>De Chadarevian</td>
<td>1982</td>
<td>M</td>
<td>1</td>
<td>TCA except skip in transverse colon</td>
</tr>
<tr>
<td>Yunis</td>
<td>1983</td>
<td>M</td>
<td>5</td>
<td>TCA except skip in transverse colon</td>
</tr>
<tr>
<td>Taguchi</td>
<td>1983</td>
<td>M</td>
<td>1</td>
<td>TCA except skip in ascending colon</td>
</tr>
<tr>
<td>Seldenrijk</td>
<td>1986</td>
<td>M</td>
<td>2</td>
<td>TCA with multiple skips</td>
</tr>
<tr>
<td>Anderson</td>
<td>1986</td>
<td>M</td>
<td>1</td>
<td>TCA except skip in ascending colon</td>
</tr>
<tr>
<td>Kapur</td>
<td>1995</td>
<td>F</td>
<td>2</td>
<td>TCA except skip in ascending colon</td>
</tr>
<tr>
<td>Yang</td>
<td>2005</td>
<td>M</td>
<td>3</td>
<td>TCA with multiple skips</td>
</tr>
<tr>
<td>Ziad</td>
<td>2006</td>
<td>M</td>
<td>2</td>
<td>TCA except skip in transverse colon</td>
</tr>
<tr>
<td>Oshio</td>
<td>2008</td>
<td>M</td>
<td>1</td>
<td>TCA except skip in ascending colon</td>
</tr>
<tr>
<td>Puri</td>
<td>2010</td>
<td>M</td>
<td>1</td>
<td>TCA except skip in transverse colon</td>
</tr>
<tr>
<td>Doi</td>
<td>2011</td>
<td>F</td>
<td>1</td>
<td>TCA except skip in transverse colon</td>
</tr>
<tr>
<td>Burjonrappa</td>
<td>2012</td>
<td>M</td>
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<td>TCA except skip in ascending colon</td>
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<tr>
<td>Moore</td>
<td>2013</td>
<td>M</td>
<td>2</td>
<td>Skip in right and descending colon</td>
</tr>
<tr>
<td>Erten</td>
<td>2014</td>
<td>M</td>
<td>1</td>
<td>TCA except skip in hepatic flexure</td>
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<tr>
<td>Ragunath</td>
<td>2014</td>
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<td>TCA with skip in ascending colon and hepatic flexure</td>
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<td>Gross</td>
<td>2015</td>
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<td>Current case</td>
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<td>1</td>
<td>TCA except skip in cecum and ascending colon</td>
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**References**