Emergence of Ectopic Adrenal Tissues - What are the Probable Mechanisms?

TARÇIN and ERCAN. Review on Ectopic Adrenal Tissues

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Abstract
Ectopic adrenal tissue, defined as the formation of adrenal tissue in an abnormal anatomical location, is not a rare entity and may have clinical significance. Even though the mechanism for their emergence has not been fully understood, numerous cases of ectopic adrenal tissues have been reported, mostly in the vicinity of the original location of adrenal gland, such as in kidneys and gonads. In these cases, their emergence was attributed to a probable migration defect by most of the authors. On the other hand, this mechanism does not simply explain the ectopic tissues in remote locations, such as hypophysis and lungs. This review brings together the reports describing many different locations in which ectopic adrenal tissues were encountered together with their speculated mechanisms.

Keywords: Ectopic adrenal; adrenocortical; heterotopia; choristoma; adrenal rest

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Introduction
Embryogenesis begins with a single cell, a newly fertilized oocyte. This cell is capable of giving rise to many different types of tissues, even extraembryonic tissues, such as placenta (i.e., it is totipotent) under certain physiological conditions. During development from zygote to a multicellular organism, cells are permanently in communication with their neighbor cells, sending and receiving molecular signals. Several intracellular signaling pathways have been elucidated, such as fibroblast growth factor (FGF), sonic hedgehog (SHH) and wingless (WNT) pathways. These signaling mechanisms enable the cells to go through an intricate series of events: proliferation, cell fate determination, survival, differentiation, apoptosis, migration, adhesion and cell shape changes (1,2). After the proliferation phase, the cells choose their particular fate and acquire characteristics of different cell lineages and subsequently migrate to their appropriate locations within the embryo. Defects in migration at all stages of development may cause severe conditions (3).

The terms “ectopia” and “heterotopia” are used interchangeably, and ectopic tissues can also be called “accessory” or “rest” tissues. They all refer to the presence of a mature tissue within another tissue due to a developmental anomaly which occurs adjacent organs during development. If heterotopic tissues aggregate and form a tumor-like mass, it is called a “choristoma”, as the suffix “-oma” is added to indicate a tumor (4,5). Morgagni, who noticed “yellowish nodules with the characteristics of adrenal tissue in the near vicinity of the gland” was the first to report a heterotopic adrenal tissue in 1740 (6). Approximately 150 years later, Marchand (7) encountered adrenal tissue remnants in fetal and infant cadavers, and speculated that adrenal cells could adhere to neighboring tissues and thereby migrate to an abnormal location during early stages of embryogenesis.

Adrenogenital Development
To better understand the mechanism of emergence of ectopic adrenal tissues, it is necessary to know about adrenogenital development. The adrenal gland has a dual embryological origin as it consists of two parts: cortex and medulla, arising from the intermediate mesoderm and neural crest cells, respectively. The adrenogenadal primordium appears as a thickening of the coelomic epithelium from about 4 weeks post conception (wpc). Adrenogenital primordium separates from the epithelium and invade the underlying mesenchymal layer of the intermediate mesoderm. The cells next to mesonephros migrate dorsolaterally to form gonadal primordium, while the more medial cells migrate dorsomedially to form adrenal primordium at 52 days post conception (dpc). Meanwhile, adrenal medulla begins to develop from neural crest. From 6 wpc, neural crest cells which differentiate into chromaffin cells migrate towards and enter the developing adrenal primordium (Figure 1). By 50-52 dpc, the inner fetal zone, forming the major part, and the outer definitive zone are detectable in the adrenal cortex. By 9 wpc, adrenal gland is encapsulated and intensely vascularized with subcapsular arterial plexus. At this time, the gland contains a cortex containing the definitive zone and fetal zone and a center containing islands of chromaffin cells. A third cortical zone, the transitional zone between the definitive zone and the fetal zone appears by 14 wpc. Subsequently, the fetal zone begins to involute and the definitive zone and transitional zone give rise to the zona glomerulosa and zona fasciculata, respectively, which mature under the stimulation of adrenocorticotropic hormone and angiotensine (8–10).

Ectopic Adrenal Tissues Contain Either Cortex Only or Both Cortex and Medulla
The adrenal rest tissues may contain only cortex or both cortex and medulla, depending on whether the fragments separate before or after medullary tissue migrates into the cortex (5). As mentioned earlier, the adrenal gland, particularly the cortex, has an anatomically close relation to the gonads during embryogenesis. Therefore, it has been postulated that adrenal rests
may descend together with the testes in males in the embryological period and contain only cortex, while the adrenal rests close to the normal location of the adrenal gland may also contain medulla. This process has been suggested for and commonly accepted as the etiology of testicular adrenal rest tumors (5,11).

As for the ectopia of adrenal medulla, chromaffin cells of the adrenal medulla and sympathetic neurons were thought to derive from a common neural crest precursors until recently (12). However, recent studies have shown that “Schwann cell precursors” (descendants of the neural crest) directly give rise to adrenal medulla (13). Also, chromaffin cells of the adrenal medulla differ from the extra-adrenal chromaffin cells in regard to their “molecular cross-talk” with the steroidogenic cells of the adrenal cortex. This interaction between adrenal chromaffin cells and cortex is essential for the maturation of adrenal medulla, whereas the Zuckerkrandl organ, the largest extra-adrenal chromaffin accumulation in mammals, lacks such interaction with a steroidogenic tissue and undergoes involution after birth (postnatal autophagy-mediated cell death) in the absence of cortex-derived glucocorticoids (14). This appears to be the reason for the absence of literature describing ectopic of adrenal medulla only (not surrounded by cortex), while entities related to adrenal or extra-adrenal chromaffin cells (pheochromocytoma and paraganglioma), and even pheochromocytoma in ectopic adrenal gland have been reported (15,16).

**Probable Impact of Adrenocorticotropic Hormone Levels on the Emergence of Ectopic Adrenal Tissues**

Adrenocortical rests are commonly found in children in the retroperitoneal area, appearing as bright-yellow nodules. These tissues are present in approximately half of the newborns and generally undergo atrophy and disappear within several weeks after birth. On the other hand, adrenocortical rests may also undergo hyperplasia under excess stimulation of increased adrenocorticotropic hormone (ACTH) secretion which may even give rise to a neoplasm. The latter mechanism has been suggested in the pathogenesis of the testicular adrenal rest tumors in patients with congenital adrenal hyperplasia, and also explains the higher prevalence of testicular adrenal rest tumors in this patient group (up to 94%) than in healthy newborns (7.5-15%, according to autopsy and surgical findings) (17,18).

Glucocorticoid replacement regimen in congenital adrenal hyperplasia is useful in the treatment by suppressing ACTH secretion and thereby regulating excess androgen secretion (19). Suppressing ACTH levels with glucocorticoid replacement has been reported to lead to a reduction in testicular adrenal rest tumor size and improve testicular functions. Concordantly, the prevalence of testicular adrenal rest tumors is higher in patients with severe forms of congenital adrenal hyperplasia who are exposed to higher ACTH levels even in utero than those with non-classic congenital adrenal hyperplasia with moderate elevation of adrenocorticotropic hormone, given the fact that adrenocorticotropic hormone receptors are found in testicular adrenal rest tumor tissues (20).

There are a number of studies and observations supporting the role of ACTH in the development of testicular adrenal rest tumors, one of which has been mentioned above, in patients with congenital adrenal hyperplasia. As with conditions in which patients are exposed to high levels of ACTH from early infancy, adrenal rest tumors have occasionally been reported in Nelson’s disease (Table 1) which is an acquired condition in later years of life associated with high levels of ACTH (20). Adrenocorticotropic hormone plays a crucial role both in the development of adrenal glands and in the regulation of cell differentiation (8). This effect of ACTH on adrenal glands has also been demonstrated in an animal research with 12-week-old mice. After an injection of tetracosactide, a synthetic peptide analogue of ACTH, cell proliferation was observed in one or both ovaries, broad ligament (26).

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**Recent Speculations on Other Possible Stimulating Factors**

In recent years, more detailed studies on the origin and characteristics of adrenal rest tumors have demonstrated that these tumors also have Leydig cell characteristics (expression of INSL3, LHCGR and HSD17B3 genes) and receptors of angiotensin I I and luteinizing hormone, as well as of ACTH. Therefore, it has been hypothesized that these tumors have an origin from a pluripotent cell type, probably from the urogenital ridge or the adrenogonadal primordium, and other factors, such as angiotensin II and luteinizing hormone may be involved as well (11,20,22-24).

**Defects during the Migration of the Precursor Cells**

Given that adrenocortical rests are thought to be derived from the urogenital ridge or the adrenogonadal primordium, it is not surprising that these issues can be found anywhere along the migratory course of the gonads, the descending path of testes and in the vicinity of the kidneys and adrenal glands. Sullivan et al. (25) conducted a study in children under the age of 16 years reporting that in 25 out of 935 groin explorations performed due to various surgical conditions, such as inguinal hernia, undescended testes or hydrocele, adrenocortical tissues were found incidentally, giving a rate of 2.7%. The absence of adrenal cortical tissue in any of the 35 girls involved in this study supports the idea that adrenocortical tissue fragments may be present in patients having adequate glucocorticoid replacement, thus with normal levels of ACTH, suggesting that ACTH level is not the only factor involved (22).

**Hypotheses on the Impact of Steroidogenic Factor-1 (SF-1, NR5A1) Overexpression**

In the early 1900s, SF-1 was first identified as a key regulator of steroidogenic enzymes (30), and later, it has been shown to control endocrine development and function as it is expressed in the adrenal gland, gonads, pituitary gonadotroph cells and ventromedial hypothalamus.
During embryogenesis, the adrenogonadal primordium is identified by its expression of SF-1. Thereafter, the fate of bipotential precursor cells is determined by their SF-1 expression levels. The cells expressing higher levels of SF-1 form gonadal primordium, while those expressing lower levels form gonadal primordium (10).

Based on mouse models, deletion of the gene encoding SF-1 was shown to cause agenesis, delayed or incomplete development of the adrenal glands, gonadal dysgenesis, abnormalities of the ventro-medial hypothalamus and partial hypogonadotropic hypogonadism, while overexpression of SF-1 has been shown to cause increased proliferation and decreased apoptosis of the adrenocortical cells resulting in aberrant proliferation and neoplasia in the adrenal tissue (8,31).

A fetal adrenal enhancer (FaDE) which initiates SF-1 expression has been identified and demonstrated to be activated in gonads, adrenal cortex and interestingly in the thorax (32). In a later study conducted with transgenic mice by the same researchers, SF-1 was overexpressed using a FaDE-SF-1 transgene, and in addition to increased adrenal size, emergence of ectopic adrenocortical cells in the thorax expressing steroidogenic markers including CYP21 was observed. This finding may help explain the few cases of adrenocortical tissues in the thorax. The same study also revealed that in the transgenic mice, gonads remained adjacent to the kidneys. The researchers speculated that emergence of the ectopic adrenal tissue in the inguinoscrotal region resulting from the overexpression of SF-1 could interrupt the separation of the gonads, and attributed this to the frequent occurrence of cryptorchidism of ectopic adrenal tissue in boys (33).

**Adrenal Rests in the Hypophysis and their Link to SF-1**

So far, there have been reported five cases of corticotroph adenoma with interspersed adrenocortical cells (34-38). Of these, 4 cases were in the pediatric age group. In Table 2, the characteristics and suggested pathogenesis causing ectopia are summarized. Although in three of these cases, the underlying pathogenesis of the misplaced adrenocortical cells were attributed to a migration defect during embryogenesis, the location of the choristoma in the hypophysis is quite distant from those ectopic tissues reported to be in the vicinity of the adrenal gland (35,36,38); thus, its emergence in the hypophysis is unlikely to stem from a migration defect. As another proposed mechanism, the emergence of the adrenocortical cells interspersed with corticotroph cells was attributed to a possible paracrine manner. The corticotroph cells were speculated to stimulate and convert the neighboring cells to adrenocortical cells (34,37). However, in only one of the five cases (37), corticotroph adenoma was found to be functional (i.e., it had endocrine activity). The most remarkable mechanism was suggested by Mete et al. (36) in 2013, pointing out a common feature between the adrenal and pituitary glands, namely SF-1 which has an important role in the development of the both glands.

Steroidogenic factor-1 is a common key molecule in the differentiation of both gonadotropic cells in the hypophysis and adrenocortical cells. Also, in case of its overexpression, emergence of adrenocortical tissue may be expected, as mentioned earlier. However, the relevant study (33) does not mention a generation of adrenal ectopia in the pituitary region. Also, in addition to SF-1, several other essential regulators, such as Prophet of Pit1 (Prop1), Homeobox protein ANF (HesX1) and Lhx3, play a significant role in the differentiation of gonadotropins in the hypophysis (39), and differentiation of adrenocortical cells is also dependent on other several regulators such as DAX1, corticotropin-releasing hormone (CRH), ACTH and WT1 (40). Therefore, the hypothesis about the effect of SF-1 solely appears to be insufficient to explain an erroneous emergence of adrenocortical cells in the hypophysis.

**Unusual Locations of Adrenal Rest Tissues and the Proposed Mechanisms**

Adrenal rest tissues have also been reported in many places other than above-mentioned organs, i.e., in the lung, mediastinum, gastric wall, liver, placenta and spinal canal. While some authors suggested a possible mechanism to explain the abnormal locations of these tissues, others either supported these hypotheses or did not present an opinion at all. The characteristics of the cases and the suggested pathogenesis for the presence of adrenal rest tissues in these abnormal locations are indicated in Table 3.

The adrenal rest tissues of all the cases listed in Table 3 involve only cortex, except for the paratracheal 5-mm lesion reported by Shigamatsu et al. (41) which contains both cortical and medullary features. Only in three cases adrenal rest tissues were reported to be clinically functional. Two cases presented with signs of virilization (42-43) and one case with Cushingoid appearance (44).

When Table 3 is examined, a few points emerge:

- In 3 out of 4 cases with adrenal rest tissues located in the placenta, it is noteworthy that the births were premature, and one of the cases had intrauterine growth retardation in addition to being premature. However, the authors did not state if the preterm births could be related to the lesion in the placenta. Only Cox and Chavrier (45) stated that adrenocortical tissue was unlikely to be responsible for intrauterine growth retardation in their report of a late preterm neonate with intrauterine growth retardation.
- In all the cases of hepatic adrenal rest tissue, the tumors were found in the posterosuperior segment of the right hepatic lobe. As some of the analyses of these reports mentioned, hepatocellular carcinomas and adrenal rest tumors cannot be differentiated without an immunohistochemical analysis due to their histological similarity. Therefore, it was suggested that adrenal rest tissues should be considered in the differential diagnosis of the tumors located especially in subsegment VII, and immunohistochemical analyses should be performed (46).
- Spinal canal is another location where a certain number of cases of adrenal rest tissues have been reported. Most of the cases were with extramedullary involvement, and presenting symptoms appear to be related to spinal cord compression, such as weakness and/or pain in the legs, lumbar pain or symptoms associated with urination depending on the affected level of the spine. The access of the adrenal tissue to the spinal canal was suggested to be via the sheath of an exiting nerve or the adventitia of an in-growing segmental lumbar artery of the aorta (47).

**Clinical Features of the Adrenal Rest Tissues**

Adrenal gland tumors, even if found incidentally in most of the cases, may be symptomatic due to mass effect, as those in the spinal canal mentioned above. This effect has a particular importance in testicular involvement in children with congenital adrenal hyperplasia. Even if the testicular adrenal rest tumors are benign, they become hyperplastic and hypertrophic under the stimulation of ACTH. Due to their location in the rete testis, they consequently cause an obstruction of the seminiferous tubules with possible azoospermia and infertility. On the other hand, these tissues have also been demonstrated to secrete
adrenocortical hormones based on the elevated hormone levels measured from the vein of the tumor compared to the peripheral blood. As already mentioned above, there have been a few cases presented with the signs of virilization and Cushingoid appearance due to the increased levels of these hormones. Briefly, even if the adrenal rest tumors are benign, they may become symptomatic due to their both hormonal function and mass effect (17,20).

**Conclusion**

Ectopic adrenocortical tissue is not a rare entity, even in the healthy population. However, the mechanism of its emergence has not been demonstrated accurately although several mechanisms have been speculated. Migration defect solely could be considered in its appearance if in some cases the ectopic adrenal tissues had not been so distant from their original location. ACTH with its endocrine or paracrine effect, SF-1 with its effect on stem cells or yet unknown factor(s) may also play a role. Further researches are required on the subject of how adrenal tissues emerge in all these ectopic locations, given their important clinical consequences.

**References**


Table 1. Gonadal masses in patients with Nelson’s disease reported in the literature

<table>
<thead>
<tr>
<th>Reference</th>
<th>Gender</th>
<th>Age at diagnosis of Cushing’s syndrome</th>
<th>Age at surgery and surgical approach</th>
<th>Interval between surgery and development of ND</th>
<th>Age at diagnosis of the tumor</th>
<th>Location of the tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamwi et al. (48), 1964</td>
<td>M</td>
<td>7 yrs</td>
<td>7 yrs, Left total and right subtotal adrenalectomy</td>
<td>1 yr</td>
<td>14 yrs</td>
<td>Left testicle</td>
</tr>
<tr>
<td>Baranetsky et al. (49), 1979</td>
<td>F</td>
<td>24 yrs</td>
<td>24 yrs, bilateral adrenalectomy</td>
<td>1 yr</td>
<td>35 yrs</td>
<td>Bilateral paraovarian</td>
</tr>
<tr>
<td>Johnson et al. (50), 1981</td>
<td>M</td>
<td>15 yrs</td>
<td>15 yrs, bilateral adrenalectomy</td>
<td>1 yr</td>
<td>23 yrs</td>
<td>Both testicles and left spermatic cord</td>
</tr>
<tr>
<td>Verdonk et al. (51), 1981</td>
<td>F</td>
<td>25 yrs</td>
<td>25 yrs, bilateral adrenalectomy</td>
<td>24 yrs</td>
<td>49 yrs</td>
<td>Bilateral paraovarian and broad ligament</td>
</tr>
<tr>
<td>Ntalles et al. (52), 1996</td>
<td>M</td>
<td>19 yrs</td>
<td>23 yrs, bilateral adrenalectomy</td>
<td>1 yr</td>
<td>29 yrs</td>
<td>Both testicles</td>
</tr>
<tr>
<td>Puar et al. (24), 2016</td>
<td>M</td>
<td>11 yrs</td>
<td>15 yrs, bilateral adrenalectomy</td>
<td>1 yr</td>
<td>27 yrs</td>
<td>Bilateral testes</td>
</tr>
</tbody>
</table>

ND: Nelson’s disease

Table 2. Adrenocortical cells reported within the pituitary gland

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age / Gender</th>
<th>Presenting complaint</th>
<th>Tumor size</th>
<th>Suggested pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oka et al. (34), 1996</td>
<td>16 / M</td>
<td>Growth retardation</td>
<td>15 mm</td>
<td>Possible paracrine effect between two cell types</td>
</tr>
<tr>
<td>Reference</td>
<td>Age / Gender</td>
<td>Presenting complaint</td>
<td>Location / Size</td>
<td>Suggested pathogenesis</td>
</tr>
<tr>
<td>----------------------------</td>
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<td>---------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Coiré et al. (38), 1998</td>
<td>18 / F</td>
<td>Amenorrhea</td>
<td>13 mm</td>
<td>Abnormal differentiation of a stem cell or misplaced adrenocortical cells during embryogenesis</td>
</tr>
<tr>
<td>Albuquerque et al. (37), 1999</td>
<td>16 / M</td>
<td>Delayed growth</td>
<td>17.5 mm</td>
<td>Possible paracrine interaction</td>
</tr>
<tr>
<td>Mete et al. (36), 2013</td>
<td>35 / M</td>
<td>Headache</td>
<td>N/D</td>
<td>Abnormal differentiation of a stem cell which might be related to SF-1</td>
</tr>
<tr>
<td>Turan et al. (35), 2021</td>
<td>11 / M</td>
<td>None, incidental finding on MRI during investigation of central hypothyroidism</td>
<td>11 mm</td>
<td>Abnormal differentiation of a stem cell or misplaced adrenocortical cells during embryogenesis</td>
</tr>
</tbody>
</table>

Table 3. The characteristics of the cases and the suggested pathogeneses for the presence of adrenal rest tissues in other abnormal locations
<table>
<thead>
<tr>
<th>Authors</th>
<th>Age</th>
<th>Gender</th>
<th>Symptoms/Conditions</th>
<th>Imaging Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sugiyama et al. (46),</td>
<td>50</td>
<td>F</td>
<td>Incidentally detected in CT performed for uterine leiomyoma</td>
<td>Segment VII of the liver / 2x3 cm</td>
<td>N/A</td>
</tr>
<tr>
<td>2015</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enjoji et al. (62),</td>
<td>67</td>
<td>F</td>
<td>None, detected in USG performed for elevated GGT</td>
<td>Segment VII of the liver / 17 mm</td>
<td>Misplaced mesothelial cells or autonomous differentiation of mesodermal elements</td>
</tr>
<tr>
<td>2017</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cox and Chavrier (45),</td>
<td>27</td>
<td>F</td>
<td>Preterm birth, intrauterine growth retardation</td>
<td>Placenta</td>
<td>During embryogenesis portion of the coelomic mesenchyme migrated, or went astray, and finally became integrated with the extracoelomic mesenchyme within the placenta.</td>
</tr>
<tr>
<td>1980</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Qureshi et al. (63),</td>
<td>30</td>
<td>F</td>
<td>Preterm birth, fetal distress, Spontaneous rupture of membranes</td>
<td>Placenta</td>
<td>Supported the hypothesis of Cox and Chavrier</td>
</tr>
<tr>
<td>1995</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guschmann et al. (64),</td>
<td>29</td>
<td>F</td>
<td>Spontaneous rupture of membranes, cervical insufficiency, preterm birth</td>
<td>Placenta / 2x1 mm</td>
<td>The primordial adrenocortical cells may enter venous vessels during migration. Thus, they might reach the blood vessels within a stem villus of the placenta via shortcuts vessels and the umbilical arteries. Cells may have gained access to the spinal canal, perhaps following the sheath of an exiting nerve or the adventitia of an ingrowing segmental lumbar artery of the aorta.</td>
</tr>
<tr>
<td>1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kepes et al. (47),</td>
<td>8</td>
<td>F</td>
<td>Bilateral leg pain</td>
<td>Spinal canal at the L2 level extramedullary / 2.5<em>1.4</em>1.3 cm</td>
<td></td>
</tr>
<tr>
<td>1990</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitchell et al. (65),</td>
<td>16</td>
<td>F</td>
<td>Intermittent pain in the thigh</td>
<td>Spinal canal at the L1-L2 level extramedullary / 1.8<em>1</em>1.5 cm</td>
<td>N/A</td>
</tr>
<tr>
<td>1993</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cassario et al. (66),</td>
<td>63</td>
<td>F</td>
<td>Burning and aching lower back pain</td>
<td>Spinal canal at the L4-L5 level extramedullary / 1.5 cm</td>
<td>N/A</td>
</tr>
<tr>
<td>2004</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karikari et al. (67),</td>
<td>27</td>
<td>F</td>
<td>Lumbar pain, gait dysfunction, impotence, sphincter dysfunction</td>
<td>Spinal canal, intramedullary / 3<em>2</em>1.8 cm</td>
<td>N/A (But supporting Kepes)</td>
</tr>
<tr>
<td>2006</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schittenhelm et al. (68), 2008</td>
<td>44</td>
<td>F</td>
<td>Bilateral leg pain</td>
<td>Spinal canal at the L1 level, extramedullary / 2.5 cm</td>
<td>N/A</td>
</tr>
<tr>
<td>Rodriguezt et al. (69), 2009</td>
<td>5-month-old</td>
<td>F</td>
<td>Weakness in lower extremities</td>
<td>Spinal canal at the T10-L2, extramedullary / 6x1.5 cm</td>
<td>N/A</td>
</tr>
<tr>
<td>2010</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Makino et al. (70),</td>
<td>17</td>
<td>F</td>
<td>Inability to crawl and stand</td>
<td>Spinal canal at the T12-L1, L3-L4 extramedullary</td>
<td>N/A</td>
</tr>
<tr>
<td>2010</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Figure 1.** Development of the adrenal cortex and the migration of the neural crest cells to form the adrenal medulla.
Figure 2. Interaction among the adrenal glands, kidneys and gonads during embryogenesis.