Pallister-Hall syndrome and McKusick-Kaufmann syndrome: one entity?

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Abstract
The Pallister-Hall syndrome is characterised by specific facial anomalies, postaxial polydactyly, imperforate anus, and brain anomalies including a dienencephalic hamartoblastoma. The hallmarks of the McKusick-Kaufmann syndrome are hydrocolpos owing to vaginal atresia, postaxial polydactyly, imperforate anus, and congenital heart defects. We report a patient with the unique features of hydrocolpos, postaxial polydactyly, and hypothalamic hamartoblastoma and discuss the different aetiological considerations of both syndromes and implications for clinical management.

Case report
The proband is the second child of healthy, non-consanguineous parents. A previously born son is normal and the family history is unremarkable. There was no drug usage or any unusual environmental conditions during the pregnancy. In the last weeks of pregnancy a cystic mass in the lower abdomen and bilateral hydronephrosis were detected by ultrasound. Delivery was normal at 36 weeks, birth weight was 3050 g, length 45 cm, and Apgar scores were 6-6-7. Multiple congenital anomalies were noted at birth including midface anomalies of a short nose, broad nasal bridge, and a small upper lip. Bilateral postaxial polydactyly and nail hypoplasia were also present. X rays of the polydactyly and imperforate anus are also typical of the McKusick-Kaufmann syndrome (MKKS). This syndrome, however, additionally shows hydrometrocolpos, hydronephrosis, and congenital heart defects.

We report here a patient with features of both PHS and MKKS.

Figure 1 Left hand with four metacarpals, partial duplication of the third metacarpal, and an accessory underdeveloped phalanx on the ulnar side.

Figure 2 Right hand with four metacarpals. The fourth metacarpal is dysplastic, the phalanges of the fourth ray are complete, and the third metacarpal incomplete and duplicated.
hands showed four metacarpals with Y shaped third metacarpals. Each end of the third metacarpals was associated with a complete digit. The left hand showed a small, underdeveloped phalanx on the ulnar side (fig 1). The right hand had a short, dysplastic, distally displaced fourth metacarpal and complete duplication of the phalanges of the fourth ray (fig 2). Instead of a separate vaginal introitus and urethral ostium only a single orifice could be found. Clinical examination showed a large, well rounded abdominal mass. A plain radiograph showed a mass arising from the pelvis, occupying most of the abdomen and displacing the intestinal gas shadows. Ultrasonographically the mass showed a good through transmission and a sharp posterior interface, suggesting a cystic lesion. The occasional scattered echoes within the cyst suggested cellular debris or mucous material. Additionally bilateral hydronephrosis and a hydroureter were detectable. The cystogram showed a small bladder which was displaced anteriorly without reflux. On the third day of life the baby deteriorated with respiratory distress because of lung compression by the mass. Simultaneously oedema and livid colouration of the vulva and both lower legs appeared as a sign of compression of the vena cava by the mass. Surgical exploration showed a cyst massively dilating the vagina (diameter 8 cm) with a small uterus located on the top. Both tubes were stretched by the vaginal mass and the ovaries were inconspicuous. After incision of the hydrocolpos 180 ml mucinous fluid was removed. Because of continuous refilling of the hydrocolpos during the first postoperative days, it had to be drained by a percutaneously inserted catheter, which interestingly drained urine. A retrograde injection of contrast material into the single orifice opacified the bladder and the hydrocolpos from the urethra, indicating a fistula between the urethra and the hydrocolpos (fig 3).

An abnormal increase in the head circumference was noted up to the ninth day. Cranial ultrasound showed a large diencephalic tumour 3 cm in diameter in the supra- and parasellar region with a homogeneous echo pattern similar to the normal adjacent brain.

![Figure 3](image1.png) Injection of contrast material in the single orifice showed a fistula between the urethra and the hydrocolpos (arrow).

![Figure 4](image2.png) Hypothalamic tumour in a medioasagittal section on cranial echography (arrows).

![Figure 5](image3.png) Moderate enlargement of the left and right ventricle in a coronal section on cranial echography (arrows).

![Figure 6](image4.png) Hypothalamic hamartoblastoma without contrast enhancement in axial section on MRI.
features of PHS

Table 1

<table>
<thead>
<tr>
<th>Features of PHS and MKKS compared with our patient</th>
<th>PHS</th>
<th>MKKS</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocolpos</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Postaxial polydactyly</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Hamartoblastoma</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Nail dysplasia</td>
<td>+</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Congenital heart defects</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Imperforate anus</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Facial dysmorphism</td>
<td>+</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Hydronephrosis</td>
<td>-</td>
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</table>

Discussion

The typical hallmarks of PHS and MKKS and the findings in our patient are summarised in the table. The main feature of MKKS is a hydrocolpos owing to complete vaginal obstruction. The hydrocolpos in our patient was caused by vaginal atresia with a vaginourethral fistula. Reed and Griscom reported one patient, and Kirks and Currarino two patients, with hydrometrocolpos caused by distal vaginal atresia like our case. Kirks and Currarino found that this type of urogenital anomaly a vaginourethral communication is common.

In both PHS and MKKS hindgut malformations are common. Hall et al reported five patients with imperforate anus in PHS. Of out 26 patients with hydrometrocolpos reported by Reed and Griscom, 12 had an imperforate anus and six had an intestinal obstruction or malfrotation. In our patient there were no gastrointestinal malformations.

The other main finding in our patient was the hamartoblastoma. Congenital brain neoplasms are very rare, especially in the diencephalic region. In 1980 PHS was described by Clarren et al as a syndrome with a hypothalamic tumour, facial, limb, and intestinal malformations. All these previously reported hamartoblastomas had the same location, growth behaviour, consistency, colour, and vascularisation as the tumour in our patient.

In PHS and MKKS hypopituitarism owing to a missing pituitary gland is common. In our patient the pituitary could not be found on MRI. However, there is no evidence for hypopituitarism, although stimulation tests have yet to be done.

The midfacial hypoplasia found in our patient is the same as reported in PHS. Another main finding of PHS and MKKS is limb malformations. Whereas postaxial polydactyly is typical of MKKS, Hall et al gave an exact description of the limb malformations in PHS, affecting the third, fourth, and fifth fingers. In particular the Y shaped third metacarpals with accessory digits in our patient point strongly to PHS. Similar limb and central nervous malformations are typical of the oral-facial-digital syndrome type VI (Varadi syndrome), but none of the characteristic facial malformations of this syndrome (midline cleft lip and palate, lobulated tongue with nodules and frenulae) could be found in our patient. Urogenital malformations are not typical of Varadi syndrome either.

Several hypotheses concerning the aetiology of PHS and MKKS have been reported. Hall et al pointed out that hamartoblastoma and imperforate anus affect the rostral and caudal end of the notochord, respectively. Since the primitive cloacal membrane differentiates into the sinus urogenitalis and the anorectal canal, the very close relation of the two affected regions is obvious. This view is thus supported by the fact that a hydrometrocolpos is frequently associated with an imperforate anus.

The simultaneous appearance of multiple malformations in different organs suggests the influence of a common agent in a certain vulnerable period of embryogenesis. The hamartoblastoma in PHS arises from the hypothalamic plate in the fifth week of gestation. As brain development induces development of the face, a disturbance of midline structures, for example, by hypothalamic tumours, leads to midfacial malformations. Further malformations in our patient, postaxial polydactyly, Dandy-Walker malformation, and
sinus urogenitalis, are caused by a disturbance between the fifth and sixth week of embryogenesis.\textsuperscript{12} Therefore a common insult during the fifth week of gestation is probable. Several authors\textsuperscript{13-3} raised the possibility of an environmental aetiological component.

These embryological considerations and the fact that the features of PHS overlap those of MKKS suggest that both syndromes are expressions of one entity. Contrary to this are the recent results of Topf et al\textsuperscript{7} and Thomas et al\textsuperscript{10} that raised the possibility of new dominant mutations in PHS, whereas MKKS is inherited as an autosomal recessive trait.\textsuperscript{11}

To our knowledge this is the first patient reported showing the combination of a hamartoblastoma and a hydrocolpos. Therefore it should be kept in mind that a neonate with hydrocolpos and polydactyly may suffer from a clinically silent hamartoblastoma of the hypothalamic region or other brain malformations. Consequently all children presenting with hydrocolpos should undergo cranial ultrasound or MRI or both to exclude such a tumour.