Association Of Single Umbilical Artery With Common And Rare Congenital Malformations

M Sur, S Nayler, R Muc

Citation

Abstract
Single umbilical artery (SUA) is the most common abnormality of the umbilical cord. It is associated with an increased incidence of atresia of hollow organs, renal abnormalities, limb reduction defects and spontaneous abortions. The aetiopathogenesis, although unknown, is attributed to vascular disruption.

In this study, 15 foetal autopsies with SUA, seen over a one-year period have been reviewed. Apart from the common associations, certain other abnormalities and syndromes, not described previously, have been identified. In addition to the well known multi-system malformations, five cases demonstrated unilateral or bilateral cystic renal dysplasia. Two of these cases had posterior urethral valves, whilst two cases showed additional features of Potter's sequence and one case showed Meckel's syndrome in association with SUA. These anomalies may have been due to obstruction to the urinary outflow, which is known to cause cystic renal dysplasia or may have resulted from ischaemia associated with SUA.

The association of SUA with these malformations, previously undocumented warrants further study.

INTRODUCTION
Single umbilical artery (SUA) is the most common developmental abnormality of the umbilical cord. The incidence of this malformation varies significantly in large series of newborns, though a range of 0.2 to 1.5% is most widely accepted. SUA is associated with multi-organ congenital abnormalities, an increased risk of premature labour, intrauterine growth retardation (IUGR) and intrauterine or neonatal death. The aetiopathogenesis, although not definitively clarified, has been attributed to vascular disruption. In this study, 15 autopsied foetuses with SUA, collected over a one year period have been reviewed and in addition to the more common associations, certain other congenital abnormalities and syndromes, not described previously, have been detected.

MATERIAL AND METHODS
Fifteen stillborn foetuses with SUA were submitted for autopsy, to the department of Anatomical Pathology, New Johannesburg Hospital, South African Institute of Medical Research and University of the Witwatersrand, over a one year period from July 2000 to July 2001. After written consent was obtained from the parents, full autopsy examinations were undertaken as was gross and microscopic examination of the placenta. Maternal history was determined from the autopsy request forms and review of clinical records.

RESULTS
The maternal ages ranged from 20–35 years. The gestational ages of the foetuses ranged from 17-36 weeks. All foetuses presented with a single umbilical artery (Figure 1).

Figure 1
Figure 1: Single Umbilical artery (SUA). Whole mount section. (H&E)
The wide range of malformations in each foetus are listed in detail in Table 1.

**Table 1: Results - Clinical and Necropsy Data for the SUA cases**

<table>
<thead>
<tr>
<th>Case</th>
<th>SUA</th>
<th>Gender</th>
<th>Cystic Renal Dysplasia</th>
<th>Potter</th>
<th>Meckel's Syndrome</th>
<th>Anencephaly</th>
<th>Meningomyelocele</th>
<th>Esophageal Atresia</th>
<th>Hydrocephalus</th>
<th>Extremity Defect</th>
<th>CNS Defect</th>
<th>Calcification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Y</td>
<td>M</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Y</td>
<td>F</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>Y</td>
<td>M</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Y</td>
<td>F</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>Y</td>
<td>M</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

In this series of 15 cases, apart from the congenital malformations commonly associated with SUA, 5 cases showed unilateral or bilateral cystic renal dysplasia (Figures 2).

**Figure 4**
Figure 2: Cystic Renal Dysplasia. Cysts surrounded by primitive loose mesenchyme (100x) (H&E)

Two of these also had posterior urethral valves. Two cases, in addition, showed features of Potter’s sequence. One case demonstrated features of Meckel’s syndrome. (Figures 3, 4, 5). Apart from three cases showing a lumbar myelocele, meningomyelocele with anencephaly and complete absence of brain (encephalo-agenesis) respectively, the central nervous system was normal in all the other cases.

**Figure 5**
Figure 3: Meckel’s Syndrome (100X) (H&E). Cysts are lined by multilayered transitional epithelium or by single layer of cuboidal epithelium
Association Of Single Umbilical Artery With Common And Rare Congenital Malformations

DISCUSSION

SUA is the most common developmental abnormality of the umbilical cord, and is frequently associated with an increased incidence of atresia of hollow visceral organs, gastrointestinal and urogenital abnormalities, musculoskeletal, cardiovascular and central nervous system malformations and limb reduction defects. SUA is also frequently associated with an increased risk of premature labour, IUGR and stillbirth. The aetiology of SUA has not been fully elucidated, however, three possible mechanisms have been suggested in the embryogenesis of SUA. Firstly, there may be primary agenesis of one of the umbilical arteries. Secondly, there may be secondary regression of a pre-existing normally formed artery, and lastly there may be persistence of the original single allantoic artery of the body stalk. Regression of a pre-existing normal artery may result from a thrombotic or thrombo-embolic event, leading to haemodynamic disturbances in foetal blood flow, ultimately leading to atresias and other anomalies. The occurrence of SUA and accompanying malformations linked to ischaemia may be attributed to a generalized or multi-focal endothelial dysfunction, that is prone to result in vascular thrombosis, leading to ischaemia. Increased coagulability may be caused by twin-to-twin transfusion syndrome, and various metabolic, immunological, genetic and infectious factors. This mechanism may have played a role in case 13, where one twin was a normal female and the stillborn twin was an acardiac monster with absence of most organ systems and gross deformities of the head, face and neck.

In our series, apart from the malformations listed in Table 1, five foetuses had cystic renal dysplasia, of which two cases were associated with posterior urethral valves. Two cases showed features of Potter's sequence and one case had Meckel's syndrome. The latter two abnormalities have not been described previously in association with SUA syndrome. The exact pathogenetic mechanism is unclear. Congenital urinary obstruction in the form of urethral atresia, posterior urethral valves or anterior urethral diverticulum may be associated with renal dysplasia. As a general rule, the more severe the obstruction, the more severe is the dysplasia. This was observed in four of the cases, each with unilateral or bilateral cystic renal dysplasia associated with obstruction in the urinary tract, either in the form of hypoplastic or absent bladder (cases 8,10), urethral atresia (case 7) or in the form of posterior urethral valves (cases 9,15).

An unique finding was the hitherto undocumented coexistence of SUA with Meckel's syndrome (case 11). Meckel's syndrome, transmitted as an autosomal recessive trait, has a highly variable phenotype. Cystic renal dysplasia is recognized as the most consistent abnormality. The other more common abnormalities include posterior encephalocele, cleft palate, polydactyly, syndactyly, ambiguous genitalia, hypoplastic bladder and cysts in the liver and lungs.

With Meckel's syndrome, as was demonstrated in case 11, the kidneys have bilateral rounded cysts ranging in size from

Figure 6
Figure 4: Meckel's Syndrome. Cysts lined by multi-layered urothelium (200X) (H&E)

Figure 7
Figure 5: Meckel's Syndrome. Normal nephrogenesis at the periphery with a cyst lined by low cuboidal epithelium. (100X) (H&E)
a few millimeters to several centimeters (Figure 3). The cysts are lined by multilayered transitional epithelium or by a single layer of low to high cuboidal epithelium (figure 3,4). The stroma is loose, abundant and foetal-like in between the cysts, with normal nephrogenesis at the periphery of the kidneys 15,16 (Figure 5).

The association of Meckel's syndrome with SUA may be due to a common aetiopathogenesis, probably due to either urinary outflow obstruction secondary to bladder hypoplasia or due to vascular insufficiency resulting in cystic renal dysplasia. However, the association may be entirely coincidental and therefore warrants further study of more cases with similar combination of malformations.

CONCLUSION
Apart from well documented associations with malformations of the urogenital tract, gastrointestinal tract, cardiovascular, musculo-skeletal and central nervous system and limb reduction defects, SUA may also be associated with cases of cystic renal dysplasia, Potter's sequence and Meckel's syndrome. These anomalies could be due to obstruction to the urinary outflow, which is known to cause cystic renal dysplasia or could have a vascular basis due to ischaemia, of which, SUA is an important marker. It is quite possible that the pathogenetic mechanism in the above malformations is multi-factorial, with SUA playing a major role. Whether the association of SUA with these malformations is statistically significant warrants further study of larger series of cases over a longer time span.

References
Author Information

Monalisa Sur, F.C.Path (S.A.), M.R.C.Path (U.K.), F.R.C.P. (C)
Division of Anatomical Pathology, Department of Pathology and Laboratory Medicine, McMaster University

Simon J. Nayler, F.C.Path (S.A.)
School of Pathology, National Health Laboratory Services, University of the Witwatersrand

Ronald S. Muc, F.C.Path (S.A.), M.R.C.Path (U.K.)
School of Pathology, National Health Laboratory Services, University of the Witwatersrand