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PULMONARY DYSPLASIA WITH RENAL MALFORMATIONS: A COMMON CONNECTIVE TISSUE DISORDER?*

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SUMMARY: Yurdakök M, Hazıroğlu R, Topaloğlu H, Tınaztepe K. (Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Pulmonary dysplasia with renal malformations: a common connective tissue disorder? Turk J Pediatr 35: 111-114, 1993.

The effect of D-penicillamine (DPA) on the development of lung and kidney tissues was evaluated to determine whether the association of lung and kidney malformation results from a common generalized disorder of connective tissue in the fetal rat.

Ten animals received a daily dose of 300 mg DPA in their drinking water during the last six days of their gestation. Ten other pregnant rats were used as controls. At the end of the gestation period all the animals were delivered by cesarean section. We found that DPA treatment during gestation caused marked growth retardation in the offspring. Although the lung weight to body weight ratios did not differ between the study and control groups, the left-kidney weight to body weight ratios were found to be lower in the study group. Histologic sections showed pulmonary dysplasia with bronchomegaly, cystic alveoli, atelectasis, vascular aneurism, perivascular loose of connective tissue, small hemorrhagic foci in the lungs and caliechtasis. We hypothesize that a common connective tissue disorder induced by DPA during intrauterine life may cause lung and kidney malformations. *Key words: caliechtasis, cystic lung disease, D-penicillamine, pulmonary dysplasia, renal malformation.*

Since it has been recognized that there is an apparent association between spontaneous pneumothorax and congenital urinary tract abnormalities in newborn infants[1] and a predisposition to pneumothorax in patients with collagen synthesis defects such as Ehlers-Danlos disease and Marfan syndrome[2], we are of the opinion that a common generalized connective tissue disorder may affect both lung and kidney development. We performed an experimental study in rats to ascertain whether an induced collagen synthesis defect could lead to changes in lung and kidney development. D-penicillamine (DPA) was used in the study to induce a collagen synthesis defect because lysyl oxidase, which contains copper as an essential component, is important in the cross-linking of collagen and elastin and its activity is impaired by DPA[3].

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Material and Methods

Pregnant albino rats with a mean weight of 245 g were used in this study. Five animals received a daily dose of 300 mg DPA in their drinking water during the last six days of their gestation. Five other pregnant rats were used as controls and received no drug. At the end of gestation, all the animals were delivered by cesarean section. The serum copper levels were found to be lower in the animals that received DPA (range, 69-87 mg/dL), when compared with the control group (range, 95-98 mg/dL). All offspring (17 in the control group and 21 in the study group) were weighed and killed by decapitation. Their lungs and kidneys were removed, weighed and examined under light microscopy.

Results

We observed that DPA therapy during gestation caused marked growth retardation and a relatively decreased kidney weight in the offspring. The hematoxylin-eosin stained histologic sections showed pulmonary dysplasia with bronchomegaly, cystic alveoli, interstitial emphysema, atelectasis, perivascular loose of connective tissue and vascular aneurisms in the lung in addition to renal caliechtasis (Fig. 1) in the offspring of DPA-treated animals. Histological changes were not observed in any of the control offspring (Table I).

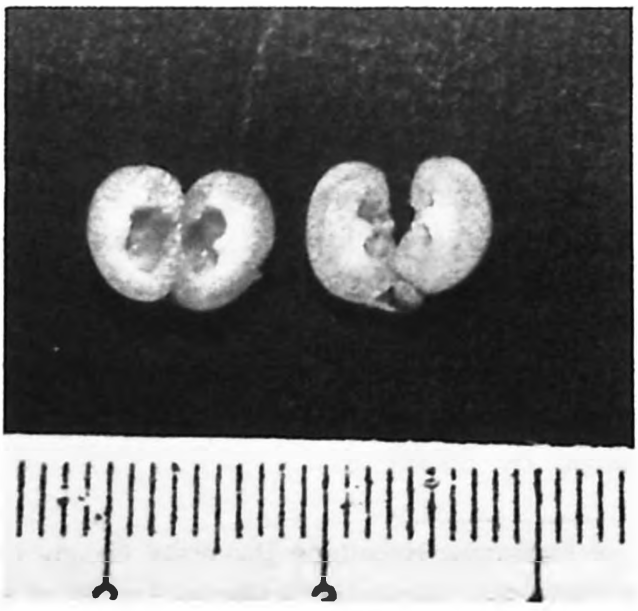

Fig. 1: Renal caliechtasis in an animal (on the left) whose mother had received D-penicillamine during pregnancy compared with the control (on the right).

Table I: The Findings of DPA Treatment During Gestation on the Fetal Kidney and Lung Tissues of Rats (mean ± SD)

	Control Group (n: 17)	Study Group (n: 21)
Body weight (mg)	9537 ± 390	8378 ± 483*
Left kidney weight (mg)	85.0 ± 9.6	60.5 ± 8.2*
LKW/BW (%)	0.89 ± 0.08	0.72 ± 0.09*
Caliechtasis		12 (57.1%)
Lung weight (mg)	258.3 ± 64.4	233.3 ± 55.6
LW/BW (%)	2.69 ± 0.57	2.78 ± 0.63
Cystic alveoli	–	17 (80.9%)

Abbr: LKW left kidney weight, LW: lung weight, BW: body weight.
* $p < 0.001$ compared with controls. Mann-Whitney *U* test.

Discussion

This study demonstrates that DPA therapy administered during gestation causes cystic alveolar lung disease and renal caliechtasis in rat offspring. Since it is known that bilateral pulmonary hypoplasia is almost always a finding in renal agenesis, and that it may also be present in diffuse and bilateral dysplastic kidneys functionally imitating bilateral renal agenesis, it has been postulated that pulmonary hypoplasia is most likely caused by increased external pressure secondary to oligohydramnios. However in cases of unilateral or bilateral renal cystic dysplasia (not the diffuse types), there have been no satisfactory explanations offered for the association of pulmonary hypoplasia with renal cystic dysplasia[1,4].

A common connective tissue disorder which involves both kidneys and lungs in an animal model is presented in this study. DPA is a powerful drug, especially since it is also a chelating agent, and therefore has wide-ranging effects. In addition to specifically inhibiting lysyl oxidase activity, it is difficult to attribute the results solely to an induced defect in collagen synthesis[5]. Therefore, additional studies are needed to support the hypothesis that a common connective tissue disorder may cause lung and kidney abnormalities.

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