Pediatr Nephrol (1991) 5: 433–435

Pediatric Nephrology

Clinical quiz

Olli Koskimies[1], Hannu Sariola[1], Christer Holmberg[1], and Juhani Rapola[2]

[1] Children's Hospital and [2] Department of Pathology, University of Helsinki, Stenbäckinkatu 11, SF-00290 Helsinki, Finland

Received October 19, 1990; accepted October 29, 1990

Case summary. A 6-day-old boy was admitted because of oedema around the eyes and in the lower extremities. He was the second child of healthy parents; the older child was a 2-year-old normally developed girl. There was no family history of renal disease in childhood.

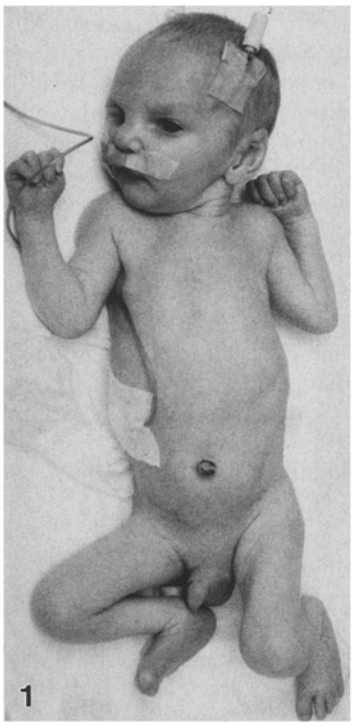
The infant had been born at term after an uneventful pregnancy; his weight was 3.3 kg, height 48 cm, and head circumference 31 cm, and the Apgar score was 10. The placenta was histologically normal and its size was 18% of birth weight. The mother noticed swelling around the eyes at the time of birth, but oedema of the lower extremities developed at 6 days. The infant was hypotonic, he had wide-set eyes, a small nose, a prominent lower forehead and his head circumference was –3.5 SD (Figs. 1, 2). The external genitals were normal. Decreased vision and hearing were suspected on clinical examination and later verified on neurophysiological examination. There were spikes in the EEG, and CT showed hypoplastic cerebellar structures. A chest X-ray showed eventration of the diaphragm.

The child was hypoproteinaemic with gross proteinuria, microscopic haematuria, intermittent glucosuria and generalized amino-aciduria. Eighty per cent of the protein excreted into the urine was albumin. His systolic blood pressure on admission was 70 mm Hg, and the serum creatinine concentration 88 μmol/l; the latter value normalized while the hypoproteinaemia was corrected with intravenous albumin and frusemide infusions. On ultrasound examination the kidneys were found to be enlarged and swollen without signs of vascular thrombosis. The acquired forms of nephrotic syndrome (NS) were excluded with serological tests for syphilis, toxoplasmosis, rubella, and cytomegalovirus infections; a chromosome analysis and an ophthalmological examination were normal.

The child was given supportive treatment and mainly tube fed to ensure a caloric and protein intake sufficient to correct for losses and catabolism. Daily albumin and frusemide infusions were needed to control the oedema. During the following weeks the infant became more hypotonic and lethargic, he vomited frequently and died at the age of 2 months without any clearly detectable clinical cause that could have explained the progressive deterioration.

Questions

1. What is the clinical diagnosis?
2. What is the histopathological diagnosis?
3. Can anything be said of the risk of recurrence in subsequent pregnancies?



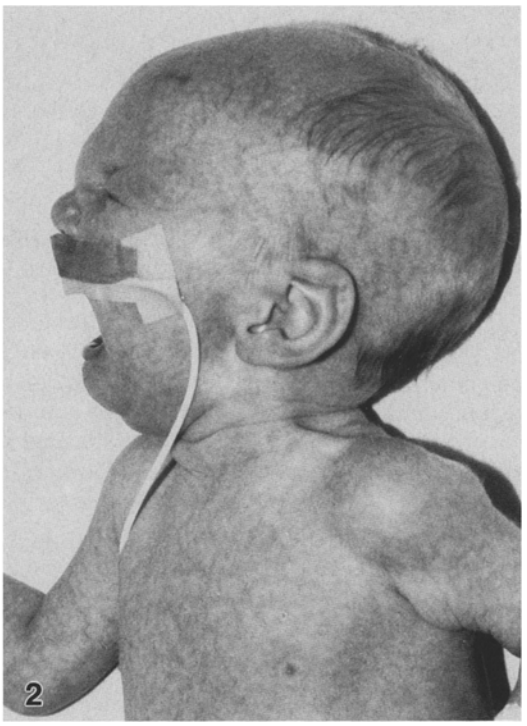


Fig. 1, 2. The infant at the age of 2 weeks. While he was tube fed and received daily albumin infusions oedema was not clearly visible

Offprint requests to: O. Koskimies

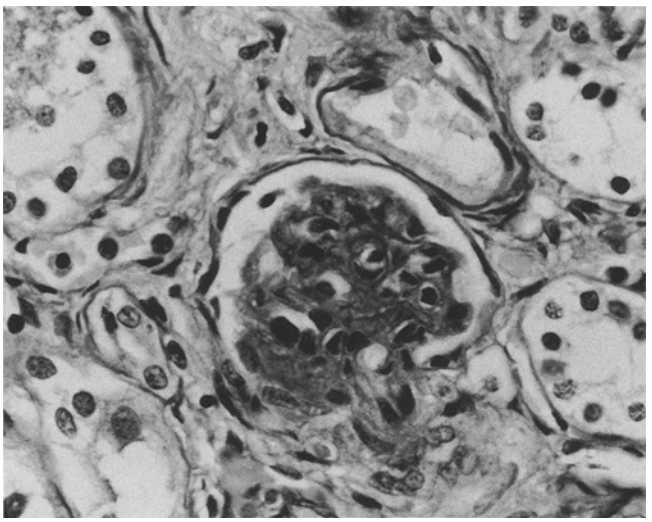


Fig. 3. Photomicrograph of a glomerulus at autopsy. Increased fibrillar mesangium, occluded capillaries and interstitial fibrosis are clearly visible. Periodic acid-Schiff, × 435

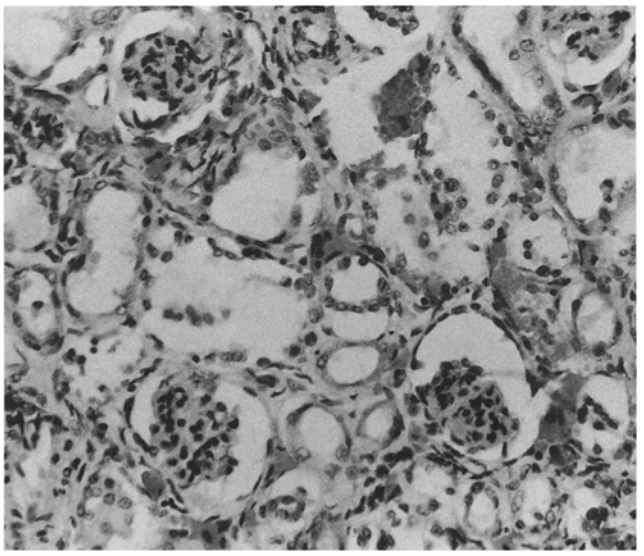


Fig. 4. Photomicrograph of the kidney at autopsy. Three glomeruli with collapsed tufts and without open capillaries can be seen. There are also atrophic tubules. Haematoxylin and eosin, × 115,5

Answers

1. Nephropathy may be associated with congenital malformations; this patient had a congenital nephrotic syndrome (CNS) in which congenital nephrosis was associated with microcephaly, brain malformations and diaphragmatic abnormality.
2. In the glomeruli typical mesangial sclerotic changes were seen, the glomerular capillary tufts were contracted and the urinary space dilated. Thus typical findings of diffuse mesangial sclerosis (DMS) were seen.
3. This triad has been reported to occur familially and an autosomal recessive pattern of inheritance has been suggested.

Commentary

The findings of oedema and heavy proteinuria at this age are typical features of CNS. CNS can be divided into acquired types, which are most often caused by intrauterine infections, and idiopathic forms, an example of which is the CNS of the Finnish type. The third group of nephrotic syndromes are those associated with malformation syndromes; a well-known example is the Drash syndrome. The infant reported here represents another entity with combined central nervous system defects and microcephaly associated with CNS.

In 1968 Galloway and Mowat [1] described two siblings with congenital microcephaly, hiatus hernia and NS. Shapiro et al. [2] reported a similar triad of findings in two out of three children in a family; the older of the affected children also had cataract and hypoplastic iris. Two other reports have been published in which central nervous system pathology was associated with NS [3, 4], these may represent partial manifestation of the same syndrome. The conclusion based on these reported families was that the disease represents an autosomal, or perhaps X-linked, recessive syndrome.

Our patient resembles these reported cases; although a hiatus hernia was not documented there was eventration of the right anterior diaphragm. On post-mortem examination the weight of the brain was 246 g (expected weight about 600 g); the most hypoplastic areas were the cerebellum and the brain stem. The kidneys of our patient showed typical DMS findings on light microscopy (Figs. 3, 4). The renal histological findings of the patients in other studies are not clear-cut [2–4]. The kidneys of the older patient of Shapiro et al. [2] were examined and focal glomerulosclerotic changes were reported; thus the microscopic changes may be similar to those seen in our patient.

The histological features of DMS appear to be relatively common in different clinicopathological disease entities associated with NS. Habib et al. [5] reported histological finding of DMS in a series of 36 patients. In 16 patients NS was the only detectable abnormality, 14 patients had Drash syndrome and in 6 patients ocular and miscellaneous abnormalities were seen in addition to NS. Our patient adds a combination of CNS, severe brain malformation and diaphragm lesion to the list of disorders associated with histological features of DMS.

The pathogenesis of DMS is not known, and because of its presence in a heterogenous population of patients with hereditary and non-hereditary disorders, it may be the end result of more than a single pathogenetic pathway. Some of these syndromes are hereditary and may be caused by a single gene with a defective product. From a practical point of view, NS associated with DMS should elicit thorough clinical investigation of the patient in order to confirm or exclude syndromic forms of NS in infants.

References

1. Galloway WH, Mowat AP (1968) Congenital microcephaly with hiatus hernia and nephrotic syndrome in two sibs. J Med Genet 5: 319–321

2. Shapiro LR, Duncan PA, Farnsworth PB, Lefkowitz M (1976) Congenital microcephaly, hiatus hernia and nephrotic syndrome: an autosomal recessive syndrome. Birth Defects 12: 275–278
3. Robain O, Deonna T (1983) Pachygyria and congenital nephrosis disorder of migration and neuronal orientation. Acta Neuropathol (Berl) 60: 137–141
4. Palm L, Hägerstrand I, Kristoffersson U, Blennow G, Brun A, Jörgensen C (1986) Nephrosis and disturbances of neuronal migration in male siblings – a new hereditary disorder? Arch Dis Child 61: 545–548
5. Habib R, Gubler MC, Antignac C, Loirat C, Gagnadoux MF (1990) Syndrome néphrotique congénital ou infantile avec sclérose mésangiale diffuse. Ann Pediatr (Paris) 37: 73–77

Book reviews

The metabolic basis of inherited disease
Edited by C. R. Scriver, A. Beaudet, W. R. Sly, and D. Valle, 6th Edition, New York, McGraw-Hill, 1990, Pp 3006, $ 215.00 (US)
ISBN 0-07-060727-3 and 0-07-060728-1.

The sixth edition of *The Metabolic Basis of Inherited Disease* represents an extensive revision of a classic textbook. Since the book first appeared in 1960, edited by Stanbury, Wyngaarden and Frederickson, it has set high standards for excellence and distinctive scholarschip in each chapter. The current edition has several significant and noteworthy features: all four editors are distinguished pediatric geneticists; the book is greatly expanded in size, being published in two large volumes of more than 3000 pages; every chapter is extensively rewritten by worldwide, senior authorities in their chosen fields; and advances in molecular biology that underpin the various inborn errors of metabolism are clearly described.

Each chapter follows a useful format. After historical aspects and clinical features of a disease or group of diseases are discussed, the biochemistry, molecular genetics and pathophysiology are clearly discussed. Although clinical details are sometimes given in summary fashion, an extensive citation of references (both historic and modern) permit the reader to gain a detailed picture of each disease. Additional strengths are elegant Tables and Figures liberally arranged throughout each chapter. The overall effect is that each chapter represents an authoritative and scholarly approach to its subject. It is a great literary source for academic physicians preparing a grand rounds presentation.

Many disorders of interest to pediatric nephrologists are discussed including: diabetes, galactosemia, disorders of amino acid metabolism, various storage diseases, nephrogenic diabetes insipidus and Fabry disease. Also covered are tubular disorders such as renal tubular acidosis, Fanconi syndrome, hypophosphatemia, and cystinosis.

Over its previous editions, *The Metabolic Basis of Inherited Disease* has emerged as one of the best medical textbooks ever written. The sixth edition carries that tradition forward and represents an extraordinary achievement in medical writing. If an individual nephrologist cannot purchase this book, they should insist that their library purchase the current edition.

Russell W. Chesney
Le Bonheur Children's Medical Center
Memphis, Tennessee 38103, USA

Hypertension: pathophysiology, diagnosis, and management. John H. Laragh and Barry M. Brenner (eds). Raven Press, New York (1990). Pp 2592, in two volumes. US $ 325. ISBN–0 881 674 931.

As the editors state in the Preface, *Hypertension: Pathophysiology, Diagnosis and management* is "the most ambitious (text) yet attempted in the field of hypertension, which has seen a swiftly accelerating interest and knowledge base over the past 25 years." Indeed, within its two volumes (2360 pages plus index, with 150 chapters written by over 250 "internationally recognized authorities and their colleagues") are buried a virtual treasure trove of classic and recent data together with relevant references spanning most aspects of hypertension. The book will no doubt take its place among major textbooks as an essential reference source on the pathophysiology and pathogenesis of hypertension. In contrast, it will be less valued as a pragmatic clinical guide, owing to the changing nature of clinical medicine and also to the rather theoretical tone of the book.

Taken as a whole, this text is a most worthwhile, perhaps critical investment for any thoughtful practitioner or researcher. The individual interested in having a luminous collections of carefully culled data that can be used as background for a research project will not be disappointed. Most of the chapters are reasonably up-to-date, and the range of topics covered is, without doubt, encyclopedic.

However, as a pediatric nephrologist, one cannot help but feel a bit left out. Though well written, the chapter on pediatric hypertension is neither startlingly new nor illuminating for the pediatric nephrology community, as it would seem that the authors were asked for a review of "pediatric issues" for internists rather than for a new synthesis. Perhaps this constitutes an unfair criticism, since this text is not written for the pediatrically inclined. Nonetheless there are topics which might have been treated more fully with good result both in the "pediatric chapter" and elsewhere. For instance, a complete chapter on coarctation of the aorta (a topic which is tucked into corners of several chapters) is really needed. Also, some focus on developmental aspects of blood pressure and hypertension would have provided some interesting food for thought concerning hypertension pathophysiology. Further comments on the genetics of hypertension from a developmentalist's point of view would have been germane.

While criticism of this giant text is easy, as a work so ambitious in scale cannot help but suffer some omissions, it has many strengths. Particularly wonderful are the chapters which discuss and even directly reproduce early classic experiments and experience about hypertension, at times in the manner of *pere et fils*. The student of primary hypertension will find just about every theory of pathogenesis and every aspects of epidemiology present. Most aspects of blood pressure regulation are covered, including some quite new data on subjects of high interest such as the roles of atrial natriuretic peptide and endothelin in hypertension.

These two volumes constitute a substantial compilation of ideas and data on hypertension. This reviewer has been toting it back and forth from laboratory to office and to home again, no trivial task, since together the volumes weight about 17 lb. It might just be worth while boying a second set.

Julie R. Ingelfinger
Harvard Medical School
Boston, Massachusetts, USA