A CLINICAL SYNDROME WITH INBORN DEFECT IN ERYTHROPOIESIS, DYSPLASTIC KIDNEYS, EYE LESIONS, MALFORMATION OF THE TEETH AND IMPAIRED HEARING

A New Syndrome in a 28-year-old Woman

Carl Ditlef Jacobsen and Erling Kruse Brodwall

From Medical Departments A and B, University Hospital, Rikshospitalet, Oslo, Norway

Abstract. A 28-year-old woman is described, having defective erythropoiesis, kidney dysplasia, minor skeletal defects, progressive loss of vision, abnormal development of the teeth and slight impairment of hearing. Her disease is most probably inherited. It started in the first years of life with thirst and weakness. From the age of 20 she had to be given blood transfusions. Kidney function has deteriorated very slowly. For many years the only feature of impaired renal function was a low specific gravity of the urine. Serum creatinine is now 2.6 mg/100 ml. Loss of vision of the left eye was noticed very early and this eye was removed when she was 12 years old because of secondary glaucoma. The other eye was later affected, and she is now blind. Very recently a slight neurogenic loss of hearing has occurred on the left side. Dental development was abnormal. The skeletal defects of genu valgum and pes excavatus were moderate. The mental, endocrine and sexual development have been normal. Her father and mother are healthy, but they have a reduced PAH and inulin clearance, indicating a slight impairment of renal function. Renal biopsy from the patient revealed kidney dysplasia with smooth muscle in the parenchyma and a lack of Henle’s loop. The cause of this syndrome and the mechanism by which all these different organ disorders can be linked together is completely unknown. To our knowledge this syndrome has not been reported previously.

Rare clinical syndromes receive great attention because they may throw light on biochemical and pathophysiological problems. Patients with symptoms and signs similar to those of such syndromes, but not definitely “typical” of one of them, are usually not classified as belonging to that particular syndrome and are therefore not published. In view of the enormous range of biochemical polymorphisms, however, it would not appear surprising that a genetic defect responsible for a certain syndrome may have different expressions in humans.

A 28-year-old woman with inborn defects in several organs, slowly increasing in severity, is described. The cause of these defects has not been found, but we nevertheless feel that this case represents either a new clinical syndrome or a peculiar variant of a known syndrome. Publication might help to obtain knowledge about similar cases.

CASE REPORT

A girl, 4 months of age, was admitted to the Pediatric Department, Rikshospitalet, because of an anemia with Hb 11.7 g/100 ml and erythrocytes 5 mill./µl. Repeated trials with oral iron were ineffective. At the age of 2 she was given a thyroid preparation because of weakness, constipation and some retardation in ability to walk. Post or propter she became more vital, but some weakness persisted. At that time her mother noticed that she often was remarkably thirsty.

At the age of 8 the thyroid treatment was stopped, as there was no evidence of endocrine dysfunction. At this time the examination disclosed a slight anemia (Hb 9.7 g/100 ml, erythrocytes 4.6 mill./µl and serum iron 109 µg/100 ml). On ophthalmological examination amblyopia was discovered in the left eye. The visual acuity was probably slightly reduced on the right side, but the eye ground was described as normal. The urine was normal. The dentist reported atypical development of her teeth.

She was readmitted when 12 years old. Just prior to that her left eye was removed due to painful glaucoma. The girl felt easily tired, complained of thirst and had episodes of colic in the abdomen. The anemia was unchanged and the specific gravity of urine was 1.008. Her ability to walk was reduced, and it was noticed that she had moderate genu valgum and pes excavatus. Caries and
periodontia were a serious problem, and a peculiar resorption of some permanent teeth had started. A prominent processus maxillaris was noted. EEG showed possible changes in deep medial structures. Air-encephalography disclosed some enlargement of lateral ventricles and 3rd ventricle, and it was concluded that she might have lesions in the region of the hypothalamus. However, her IQ and sexual development later on were normal. Ophthalmological control disclosed vitreous opacities and some minor changes in the macular region. I.v. pyelogram was normal. There was no evidence of urinary tract infection.

The patient was admitted to Medical Department A at the age of 18. She had prior thereto been treated for pain in the eye, and the fundus showed exudations and bleeding. An attack of abdominal pain was misinterpreted as appendicitis, and a normal appendix was removed without complications. As found earlier, the Hb content in the erythrocytes was reduced despite a normal serum iron; Hb 8.8 g/100 ml and erythrocytes 4.5 mill./µl. Serum creatinine was 1.6 mg/100 ml and specific gravity of urine 1.009.

The following course was a slowly progressing chronic disease. She became blind and had no benefit of extraction of a cataract. Her thirst became less (unfortunately!) and from the age of 19–20 she had to be given blood transfusions. Due to her loss of vision and tendency to diziness she does not tolerate Hb values below 8 g/100 ml. In the last 3 years she has had attacks of right-sided abdominal colic starting in the right lumbar region and irradiating to the right inguinal area. The abdomen was tender in the region of the right kidney and the clinical condition was suggestive of urolithiasis. Urological examination, examination of urine and retrograde pyelograms were normal. On one occasion she also had similar pain in the left side. Spasms in the bundles of smooth muscle in the kidneys might perhaps be the cause (see below). Evidence of epilepsy has not been found. EEG showed only slight generalized cerebral dysrhythmia.

The patient has now finished her training at the School for the Blind. During this training her normal intellectual functions were evident.

**CHARACTERIZATION OF THE VARIOUS ORGAN INVOLVEMENT**

**Anemia.** The first complete hematological investigation was performed at the age of 18. The anemia has been hypochromic, with MCH of 23–27 pg, her peripheral blood showing slight anisocytosis and a few Target cells, otherwise normal red cell morphology. In the last year the MCH has approached normal values. Her bone marrow has been cellular, showing an increase of normoblastic erythropoiesis and no signs of ringed sideroblasts. Due to the transfusions there has been an increased amount of hemosiderin in the marrow. Thrombopoiesis and granulopoiesis are normal, and there have always been normal WBC and differential counts, normal platelet counts and normal score for leucocyte alkaline phosphatase. Both megacaryocytes and platelets appear normal, and neither clinically nor by laboratory test has any bleeding tendency been found. Despite the hypochromic anemia her serum iron has been normal or slightly elevated (180 µg/100 ml) with transferrin in the normal range (280 µg/100 ml). The reticulocyte counts were usually 3–20%.

Serum haptoglobin, LDH and bilirubin values were normal on several occasions, and the half-life of Cr²⁺-tagged own erythrocytes was 28 and 32 days, examined with 7 years' interval. The erythrocytes have normal osmotic fragility. The spleen has never been enlarged. Serum B₁₂ was normal, but folic acid low (serum 1.5 ng/ml and RBC 77 ng/ml). Hb was type A on electrophoresis. There was no evidence of deficiency in intra-erythrocytic enzymes. (Elaborate studies performed by Dr M. Hjelm, Uppsala, Sweden.) Agarose gel electrophoresis of serum showed normal transferrin band. Coproporphyrins in erythrocytes were 0.1–2.0 and protoporphyrins 0.4–6.0 µg/100 ml (normal values). The excretion in urine of these substances was normal. Serum GOT and GPT and alkaline phosphatase values were within normal range, but in the last 2–3 years there has been a tendency to slightly elevated alkaline phosphatase levels. We have not had the possibility to measure hemoglobinase. Sucrose test and examination for hemosiderin in urine were normal. Serum electrophoresis, immunquantitation of immunoglobulins in serum, cholesterol, triglycerides, phospholipids, and phospholipid fractions in plasma and erythrocytes revealed no abnormality. Electroletes in serum were always normal, but in the last year an increase in phosphorus to 5.1 mg/100 ml has occurred.

**Kidneys.** Lack of ability to concentrate the urine was the first sign of kidney disease. For many years the urine was otherwise normal. Episodes of urinary tract infections in the last years might be responsible for the slight proteinuria now present. She has always had normal BP.

At the age of 25 and 28 the following renal function studies were performed: in April 1968 inulin clearance was 33 ml/min, renal plasma flow 328 ml/min, renal blood flow 444 ml/min, oxygen consumption 6.4 ml/min and citrate clearance 9.27 ml/min (normal values for these parameters are 120–140, 55–700, 900–1 200, 17–22 and 30–35, respectively). In April 1971, 3 years later, the studies revealed a progressive impairment of renal function. Inulin clearance 15, renal plasma flow 203, renal blood flow 261, oxygen consumption 2.4 and citrate clearance 4.66. In April 1968 the extraction rate of PAH was 54% (normal 88–94%). (The results are average values of 2–3 periods of 15–20 min duration.) The pyruvate-lactate ratio was normal. These studies indicated that the glomerular involvement was more advanced than the damage to the renal vascular system. Early polyuria and a better conservation of the glomerular ultrafiltration and vascular system than of the tubular function, interpreted by extraction rate of PAH at the first examination, indicated a more advanced tubular damage. These results corresponded well with the histopathological findings in the renal biopsy. I.v. pyelograms have demonstrated kidneys of approximately normal size, with normal pelvis and drainage. Light microscopic examination of the kidney biopsy revealed bundles of smooth muscles in the renal parenchyma, and the loop of Henle could not be found (Fig. 1). Amyloid deposits were absent. Most of the tubuli seen in the preparation had the appearance of collecting tubules. The embryological evaluation of the kidney
biopsies was performed by Dr H. Stalsberg, Department of Pathological Anatomy, University Hospital, Ullevål Hospital, Oslo.

Ocular involvement. A divergent squint of the left eye was present from 1 year of age. When she was 7 years old, unilateral left-sided myopia of $-13$D was found, while the right eye was emmetropic. Visual acuity at that time was: right eye: 6/6, left eye: counting fingers. At the age of 11 posterior subcapsular opacities and vacuoles in addition to vitreous opacities were found. At that time she had iridocyclitis with "iris bombe" and secondary glaucoma. The left eye was removed due to pain, but the right was normal. However, a few months later minor vitreous opacities were found, the optic disc was edematous nasally and the macular region was slightly affected. At the age of 18 her right eye was examined because of floating opacities. There was a slight uveitis, posterior capsular opacities of the lens, retinal hemorrhages and soft and hard exudates. There was a secondary glaucoma caused by a low grade chronic uveitis. Gradually, in the course of years, a posterior cataract developed and the lens was removed. She is now practically blind. Histologically, the left eye showed features of a chronic uveitis. The iris was atrophic, with infiltration of lymphocytes and some mast cells. A marked gliosis was found in retina, there were degenerative changes of the ganglial cells, hemorrhages and exudation of lymphocytes and granulocytes. The optic nerve was normal. The histological examination of the eye was performed by Dr K. Arnesen, Department of Pathological Anatomy, University Hospital, Ullevål Hospital, Oslo.

Skeleton. At the age of 8 normal structure and growth zones were found on X-ray of cranium and feet. Later she grew normally, but has a moderate degree of genu valgum and pes excavatus. Her palatum durum is high and narrow. X-ray of cranium is normal.

Teeth. Already as a child it was noted that the processus maxillaris was very prominent and that her teeth were abnormal. She got her first tooth at 9 weeks and had all her teeth at 9 months. The permanent teeth appeared already at the age of 3 and were complete at the age of 6. At the age of 12 it was noted that an abnormal resorption of the roots had started. Marked periodontia and caries were present and she had lost several permanent teeth. The malformation involved the mesodermal part of the tooth and it was described as to some extent similar to that in osteogenesis imperfecta. One of the most prominent signs was the gracile, curved...
roots. The teeth had normal density and colour. Resorption of the alveolar process was marked.

**Hearing.** When a few years old she had some episodes of otitis media. In the last 3 years she has noticed slight difficulty in hearing. At the age of 26 audiological examination was performed. Clinically the ear-nose-throat examination was normal. On the left side a neurogenic loss of hearing was found, cochlear type audiogram, similar to that found in patients with Mb. Menière.

**Other examinations.** At 26 years of age she had a period of arthralgia in upper extremities and elevated ESR. This subsided without treatment. Examinations of chest organs, liver and gastrointestinal tract have been normal. She has a tendency to gain weight. Except for hemosiderin accumulation, the liver biopsy is normal. Her sexual development has been normal, and her menstruation was regular, except for minor irregularities at the age of 25. Chromosome studies were performed at two different laboratories, both with normal count and appearance. She has several times been examined for possible endocrine dysfunction, but always with normal result. Uptake of isotope-I was normal, and excretion of corticosteroids and aldosterone in urine have been normal. Both peroral and i.v. load with glucose were normal. Wound healing is normal with normal skin. Acid-base disturbances have never been recorded. A recent EEG revealed slight generalized cerebral dysrhythmia, otherwise normal. Chromatography of urine did not reveal abnormal metabolites, and elevated levels of known metabolites have not been found on multicomponent analysis.

**Family studies.** Both father and mother were clinically healthy and had normal hematological status, electrolytes, urine, and normal serum creatinine. However, both inulin and PAH clearance were abnormal in both parents. The mother was examined in 1968 and had inulin clearance of 67–71 ml/min and PAH clearance of 394–363 ml/min. The father was studied in 1971 and the values were 53 and 293, respectively. His citrate clearance was 27.71 ml/min. Ophthalmological examination and hearing were normal in both parents.

**Therapeutic trials.** For 2 years she tried prednisone, highest dose 10 mg daily, without effect, and the local treatment of the eye lesions with steroids was also unsuccessful. Injections with various kinds of vitamins B or transfusions with fresh plasma had no effect on reticulocyte count or Hb. Neither had folic acid in 0.5 mg oral dose any effect. The silent and recurring infection of the urinary tract during the last years has been treated according to bacterial sensitivity. Despite the great number of transfusions, no transfusion reactions have occurred.

**DISCUSSION**

To our knowledge similar cases have not been reported previously. This syndrome may theoretically be explained as either a new inborn error of metabolism or a variant of a known inborn disease. Alport’s syndrome, familial hereditary nephropathy, is characterized by early albuminuria, deafness and eye affections (1, 7, 8, 10). The histological picture of the kidney in our patient, together with the hypochromic anemia and the late albuminuria, does not fit this diagnosis. For the same reasons we could not make the diagnosis of a Fanconi anemia. The eye lesions per se might fit the diagnosis of tuberous sclerosis. However, there was no other manifestation of that disorder. Lowe’s syndrome results in deficiency, typical EEG pattern and aminoaciduria with acidosis. These patients are nearly all boys, and a recessive defect located on the X chromosome has been proposed (4, 5). It must be questioned whether our patient, being female, might suffer from a partial expression of such a genetic defect. The histological feature of the kidney in Lowe’s syndrome, however, is different from the dysplasia described in our patient.

Our patient may have an inborn error in the development of the kidneys, with the other defects as secondary manifestations. Renal insufficiency usually leads to normochromic anemia being severe only with marked depression of kidney function, and our patient had a rather slow deterioration of kidney function. Furthermore, her eye lesions could be correlated neither to kidney function nor to hypertension. Her BP remains normal. Erythropoiesis levels in our patient corresponded to the degree of renal function impairment (performed by Dr S. Halvorsen, Pediatric Research Institute, Childrens Hospital, University Hospital, Rikshospitalet, Oslo). It is unlikely that all the other manifestations are secondary to a primary dysplasia of kidneys.

Our patient always had a reduced corpuscular Hb concentration and later also a reduced number of red cells. Perhaps the incorporation of iron in heme is impaired. This might indicate an enzyme deficiency. Known deficiencies in erythrocyte enzymes usually demonstrate hemolytic anemia, but our patient had normal red cell survival and no definite changes in red cell morphology. Other possibilities include abnormalities in transferrin or in binding of iron to it (2). On electrophoresis, transferrin in our patient appeared normal, and due to the many transfusions it was impossible to study the function of transferrin in this patient. Congenital dyserythropoietic anemia (3, 6) was excluded because the characteristic cytopathology of nucleated red cells was not found. Normal plasma might stimulate globin...
synthesis (9), but plasma transfusions in our patient were ineffective.

Not being able to pinpoint the cause and pathophysiology of this new syndrome, we feel that this inborn error (or, better, system of errors) may have a common etiological background, a genetic defect. Since an asymptomatic defect in kidney function was present in both parents, it is possible that our patient is homozygous for this genetic defect.

REFERENCES