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Teaching cases

Meningocerebral angiodysplasia with metanephric induction failure: Broadening the spectrum of an emerging maldevelopmental syndrome

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ABSTRACT

The uncommon simultaneous occurrence of an exuberant, angioma-like proliferation of superficial cerebral microvessels along with absence of the kidneys has been proposed to constitute a syndromic complex for which the term "meningocerebral angiodysplasia (or angiomatosis) with renal agenesis" (MCA-RA) is being descriptively used. We observed this constellation in one of a pair of dichorionic male twins following postpartal death in the 38th week of pregnancy. General autopsy revealed rudimentary metanephric *anlagen* made up of few residual glomeruli, cysts lined by flattened tubular epithelium, and islands of cartilage – corresponding to renal aplastic dysplasia. Largely inconspicuous with respect to its gyral pattern, as well as the configuration of the ventricular system, the brain microscopically showed extensive replacement of the cortex by a lattice of proliferating capillaries with necrosis of the intervening parenchyma. Minute foci of calcified necrosis were scattered in the deep subcortical white matter as well, while the ventricular ependyma and the subventricular germ cell layer remained remarkably intact. The cerebellum and brain stem appeared unaffected as well. Karyotyping of skin fibroblasts indicated a normal chromosome set of 46XY without gross structural anomalies. We interpret these findings as ones apt to being reasonably accommodated within the spectrum of MCA-RA. Although exceedingly rare, accurate identification of individual cases of MCA-RA is relevant both to differential diagnosis from its prognostically different look-alike "proliferative vasculopathy and hydranencephaly-hydrocephaly" (PVHH), and to refine the nosology of unconventional pediatric vascular malformations, for which the rather nonspecific label "angiodysgenetic necrotizing encephalopathy" is still commonly used.

1. Introduction

Vascular malformations (VMs) of the central nervous system (CNS) are hemodynamically redundant aggregates of blood vessels which may individually exhibit capillary, arterial, venous, or cavernous architecture [4,13]. Mostly congenital in origin – some of them occurring in a syndromic context – they have been traditionally categorized as capillary teleangiectasis, arteriovenous malformation, venous angioma, and cavernous angioma. In addition, massive dilation of the vein of Galen has been recognized as a peculiar form of arterio-venous shunt in neonates.

In clinical parlance, it has become customary for infantile VMs of the CNS to be subdivided into either Galenic or non-Galenic type of anomalies [2]. Besides pediatric examples of conventional VMs, however, the latter group of such typology will also semantically include some rare maldevelopmental conditions of the CNS vascular *anlagen*, whose pathogenesis and clinical consequences obviously cannot be accommodated within classical non-Galenic type VMs.

Characterized by a profusion of capillary-type and medium-sized blood vessels within the supratentorial meninges and cortical parenchyma with attendant tissue destruction, these anomalies may be descriptively referred to as "angiodysgenetic necrotizing encephalopathies" [1,19]. With but a handful of case studies on record, two consistent patterns are seen to be emerging: (i) Fowler's syndrome: profound destruction of cerebral tissue through pervasive glomeruloid capillary proliferation causing early lethality in a hereditary setting; (ii) sporadic meningocerebral angiodysplasia with variable extent of cortical and white matter necrosis and renal agenesis [3,6,8–10,16,23].

In the following, we describe macroscopic, histological, and immunohistochemical findings in a case of sporadic meningocere-

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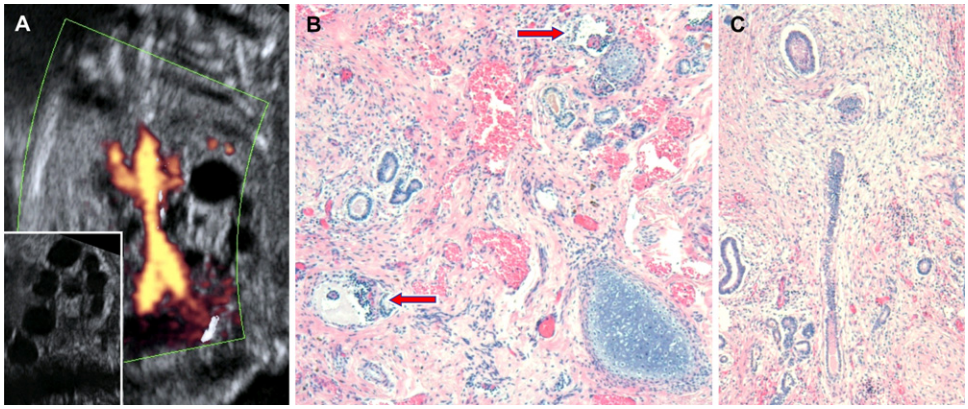

Fig. 1. *In utero* imaging and *post mortem* histological findings of kidneys with aplastic dysplasia. (A) Prenatal color-coded Doppler ultrasonography of fetus B at gestational age 20 weeks to show right kidney being progressively replaced by multiple hypoechogenic smooth-walled cysts. By 25 weeks (inset) only paperaceous-thin remnants of renal parenchyma subsist. (B) At autopsy, few collapsed glomerular tufts within cystically dilated Bowman's capsule (arrows) attest to the presence of rudimentary renal *anlagen*. Incongruous islands of hyaline cartilage are noted. (C) Persistence of blastema-like loose connective tissue around tubuli may be read as a direct reflection of failed metanephric induction. H.E. stain; original magnification: (B and C) ×60.

bral angiodysplasia. The fourth reported occurrence altogether, this case is the first to involve twin pregnancy and cystic dysplasia of rudimentary kidneys.

2. Case reportClinical history

The 28-year-old primigravida was admitted to the Department of Gynecology and Obstetrics of University Hospital (Inselspital) Bern for induction of labor in the 38th week of a dichorionic twin pregnancy. In neither of the parents' family history had been any indication of genetically transmissible malformations, nor did the mother report on previous miscarriages. Serological tests revealed either negative results (Syphilis; HIV; Toxoplasma; Hepatitis B) or indicated normal active immunity (Rubella; EBV; Parvovirus B19; Varicella). At mid-gestation, one of the fetuses had been diagnosed with severe intrauterine growth retardation, oligohydramnios, and cystic hypoplasia of both kidneys (Fig. 1A). Following induction of labor using misoprostol and oxytocin, a normally developed male fetus A was delivered, and showed uncomplicated adaptation (Apgar score: 8-9-10). Delivery of fetus B proceeded by pelvic presentation. The informed parents did not wish for life-maintaining measures to be attempted, and the newborn died 2 h post-partially while receiving palliative care. Karyotyping of cultured skin fibroblasts indicated a numerically and structurally normal chromosome set of 46XY. The autopsy findings of fetus B are the subject of the present report.

3. Materials and methods

Post mortem examination was carried out according to a standardized protocol for fetal autopsy [7]. Following fixation *in toto* for 2 weeks in 10% formalin added with 15% alcohol, the intracranial parts of the CNS were dissected in 5–6 mm frontal slices. Permission to remove the spinal cord was not obtained.

Tissue blocks were routinely processed to paraffin, serially sectioned, and 3 μm slides were stained with hematoxylin and eosin (H.E.), Gomori's silver (Ag) impregnation method for reticulin, and Prussian blue for iron (Fe). Staining with periodic acid – Schiff's reagent (PAS) was done on paired serial sections from representative cortical samples with and without diastase pretreatment. Immunohistochemistry was performed on selected brain tissue blocks with the following panel of antibodies: GFAP (clone 6F2; Dako, Glostrup, Denmark), von Willebrand factor (rabbit, polyclonal; Dako), smooth muscle actin (clone 1A4; Sigma), CD34 (clone QBend/10; Dako), collagen type IV (clone 8C5 5A5; Dianova), and CD68 (clone PG-M1; Dako), according to established protocols in our laboratory, the details of which have been documented previously [22]. Slides were developed with polymer-bound horseradish peroxidase (Envision+; Dako) and 3,3′-diaminobenzidine as chromogen.

3.1. Pathological findings

General autopsy confirmed severe intrauterine growth retardation of the male fetus, as reflected by crown-heel-length (40 cm) and body weight (1760 g). Neither dysmorphic traits nor cutaneous vascular nevi were noted. While the respective weight of most visceral organs tended to parallel the overall degree of growth retardation (i.e., corresponding to approx. 33rd to 34th week's gestational age), the lungs appeared overtly hypoplastic (22 g). Most notable, however, was the minute cumulative mass of the kidneys (3.7 g) – more properly of the flaccid tissue nodules that were dissected from the corresponding area of the retroperitoneum. Histologically, these rudimentary *anlagen* consisted of few scattered glomeruli and renal tubuli – some of them grotesquely dilated – as well as blastema-like connective tissue, and an occasional island of hyaline cartilage (Fig. 1B and C).

The fixed brain weighed 298 g (weight range appropriate for gestational age: 283–332 g). On external inspection, gyral landmarks appropriate for gestational age (i.e., all primary sulci, including the precentral, parieto-occipital, superior, inferior temporal sulci, etc.) could be identified, albeit appeared partially clouded by reddish-brown discoloration of most of the leptomeninges. Frontally sectioned slices were conspicuous for the presence of multiple segments of slightly collapsed cortical relief wherein thinning or outright laminar necrosis of gray matter was apparent (Fig. 2A). Within the stretches of affected cortical ribbon, the depth of sulci frequently showed hemorrhagic imbibition. Throughout the depth of the centrum semiovale, some minute yellowish to chalky-white speckles were noted. These changes tended to be somewhat more pronounced in the parieto-occipital region. Conversely, neither cavitating necrosis nor ventricular enlargement was seen.

Microscopically, the subarachnoid space of the areas involved was slightly distended by dilated capillaries of varying diameter, as well as ectatic veins, both gorged with erythrocytes (Fig. 2B and C). While penetrating the pial boundary, those vessels were seen to abruptly assume remarkable uniformity, henceforth giving rise