

CASE REPORTS

## Cleidocranial Dysplasia with Neonatal Death Due to Central Nervous System Injury in Utero: Case Report and Literature Review

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### ABSTRACT

Cleidocranial dysplasia (CCD), an uncommon disorder involving membranous bones, is rarely lethal in early life. The calvaria is defective and wormian bones are present. Abnormalities of the clavicles vary in severity from a minor unilateral defect to bilateral absence. This report concerns pre- and postmortem anatomical and radiological findings in a 15-day-old female neonate with CCD. Her postnatal course was characterized by seizures and recognition of hydrocephalus during the first day of life. The calvaria was hypoplastic with numerous wormian bones. A pseudofracture of the right clavicle was present. Hydrocephalus was present in the brachycephalic brain which had a severely thinned cerebral cortex. Hemosiderin in the ventricular lining and marked subependymal gliosis were interpreted as evidence of old intraventricular hemorrhage that had occurred in utero. A CCDrelated condition, Yunis-Varon syndrome (YVS), is noted for early lethality and for developmental and secondary abnormalities of the central nervous system. The present case only partially matches the phenotype of YVS and might represent a part of a spectrum of phenotypic variants ranging from viable CCD to lethal YVS.

**Key words:** cleidocranial dysplasia, wormian bones, neonate, hydrocephalus, pseudofracture of clavicle

#### INTRODUCTION

Cleidocranial dysplasia (CCD), also known as Marie-Sainton disease and formerly called cleidocranial dysostosis, is an uncommon disorder of the skeleton with prominent abnormalities of membranous bones, especially the skull and clavicles. Early lethality is rare. We report a neonate with death at 15 days secondary to in utero insults to the central nervous system.

### CASE REPORT

This female neonate, who died at 15 days of age, had been delivered vaginally at 37 weeks of gesta-

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tion by a 29-year-old mother who had undergone treatment for Hodgkin's disease 3 years previously. The prenatal course of this pregnancy was uneventful. Maternal glucose tolerance was normal. AFP screening was refused. The 1980 gram infant had Apgar scores of 2 and 3 at 1 and 5 min, respectively, and required intubation. Dysmorphic features were noted. X-rays revealed abnormal skull and right clavicle and 11 ribs bilaterally. The course was complicated by hypoglycemia, diuresis with hyponatremia, intraventricular hemorrhages, and thrombocytopenia. Seizures began shortly after birth. An electroencephalogram showed lateralized discharges from the right occipital region. Ultrasound examinations performed on day 1 of life revealed moderate hydrocephalus and dilatation of the renal collecting systems. The latter abnormality was thought secondary to clinically evident diabetes insipidus. A cranial CT scan on day 4 showed moderate dilatation of the lateral ventricles, greater in the left lateral ventricular body and temporal horn. The third ventricle was mildly dilated. Though the presence of blood was not documented on the study, hydrocephalus was considered to be secondary to previous intraventricular hemorrhage. An MRI on day 8 confirmed these findings and revealed brachycephaly and a thin corpus callosum. Karyotype determined from lymphocytes was 46,XX.

### PATHOLOGIC FINDINGS

Postmortem examination revealed the following measurements: head circumference 28.1 cm, crown-rump length 31.5 cm, crown-heel length 40.8 cm, foot length 6.25 cm, and chest circumference 28.2 cm. The body weighed 2164 grams. Dysmorphic craniofacial features included a small, round skull with thin, flexible bone. The fontanelles were confluent and large with the space partially occupied by wormian bones forming a mosaic pattern. Micrognathia, narrow palpebral fissures, and a wide nose with anteverted nostrils were present (Fig. 1). Arthrogryposis in the distal upper extremities and bilateral talipes equinovarus were noted. X-rays revealed a pseudofracture in the midportion of the right clavicle and confirmed wormian bones in the skull (Fig. 2a,b). Lateral view of the skull allowed only poor visualization of the

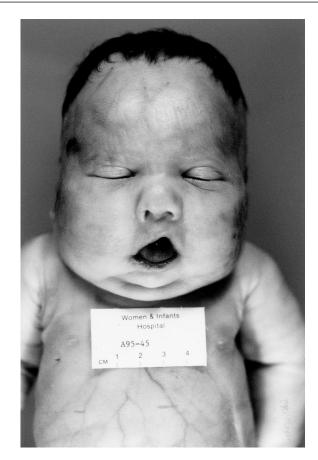
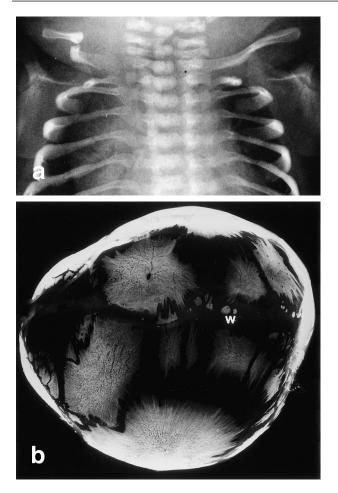


Figure 1. Dysmorphic features included a small, round skull, micrognathia, and anteverted nostrils.

clivus due to superimposition of the dense petrous portion of the temporal bone.

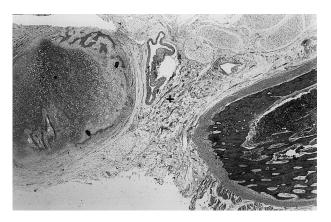
There were a few pleural petechiae. Mild hydronephrosis was noted on the right. The bladder and ureters were dilated but free of obstruction. As the calvaria was removed in a circular manner, the thin cerebral cortex was lacerated and a large amount of serosanguinous cerebrospinal fluid escaped under pressure. The brain was brachycephalic. After fluid removal, it weighed only 160 grams (reference weights  $337 \pm 91$ ). The cerebral cortex was markedly thin, especially in the posterior parietal, temporal, and occipital regions. The white matter was extensively attenuated. The deep gray structures, including basal ganglia, thalami, and hippocampi were not identifiable. All ventricular chambers were markedly dilated. The ventricular lining was thick and brown with small focal collections of blood. The brainstem and cerebellum were well formed. However, the basis pontis was slightly flattened and the pyramids were symmetri-



**Figure 2.** a: X-ray showing pseudofracture of right clavicle. b: X-ray of removed upper portion of skull with anterior portion to the left in the photograph. Note wormian bones (w).

cally small. A small, recent parenchymal hemorrhage was noted in the left lobe of the cerebellum.

Microscopically, the right clavicle consisted of two disconnected portions of tubular bone. The space between the two portions of bone contained an abnormal area of fibrovascular connective tissue. The portion nearest the sternum was essentially normal. The lateral portion had a disorganized surface, simulating a growth plate, with zones of proliferation, calcification, and endochondral ossification arranged in a haphazard fashion. The cartilage, however, was hypertrophied and disorganized with haphazardly arranged foci undergoing enchondral ossification (Fig. 3). The process was interpreted as dysplastic rather than representative of a healing fracture. The bone of the calvaria was histologically undergoing normal membra-



**Figure 3.** Photomicrograph of midportion of right clavicle. The abnormal lateral portion is on the left; the relatively normal medial portion is on the right. The two portions are separated by intervening fibrovascular connection (+). Objective magnification  $\times 2$ .

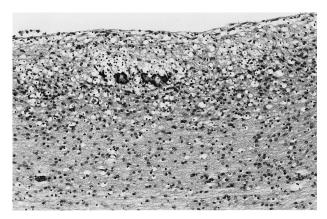


Figure 4. Photomicrograph of lining of lateral ventricle. Surface epithelium is absent. The subependyma shows ependymal rosettes and gliosis. Objective magnification  $\times 20$ .

nous ossification. The abnormality was quantitative with increased amounts of fibrous tissue connecting the islands of membrane bone.

The cerebral cortex showed normal laminar architecture but with extensive hypoxic/ischemic damage consisting of pericellular vacuolation, nuclear pyknosis, and gliosis. The white matter was attenuated with extensive fibrillary astrocytosis confirmed by immunostaining for glial fibrillary acidic protein. The ventricular lining was multifocally disrupted and in many subependymal locations gliosis and occasional ependymal rosettes were present (Fig. 4). Hemosiderin was noted and confirmed by stain for iron (Prussian blue). Small periventricular cysts were seen in the frontal region. Hypoxic/ischemic changes were present in the basal ganglia, brainstem (including cranial nerve nuclei), and cerebellum. The pyramidal tracts were atrophic, most likely secondary to extensive white matter destruction. The spinal cord, including the anterior horn cells at all levels, showed mild to moderate hypoxic/ischemic changes with no neuronal loss as compared with two age-matched controls. No microglial nodules or inflammatory infiltrates were seen. The small recent hemorrhage in the cerebellum was confirmed. These neuropathological findings were consistent with severe hydrocephalus secondary to old hemorrhage, severe telencephalic leukoencephalopathy, diffuse hypoxic/ischemic changes, and recent focal hemorrhages. With no evidence of developmental malformation, all abnormalities were thought to have been acquired secondary to insult(s) beginning in utero, an interpretation supported by the clinical recognition of hydrocephalus on the first day of life.

#### DISCUSSION AND REVIEW

Clinical, radiological, and pathological findings in this neonate are consistent with cleidocranial dysplasia (CCD), a condition with abnormal development of membranous bones. Membranous bones are formed via a collagen model and include the neurocranium, a portion of the clavicles, and some facial bones including the mandible. In CCD, first described in the late 19th century [1], the calvaria shows generalized failure of midline ossification. Wormian bones are present. A term newborn with CCD has a skull comparable to that of a normal fetus in the midtrimester [2]. The condition is usually associated with viability. The skull undergoes gradual postnatal mineralization but some defects persist for at least the first 7 years [2]. Non-union of the mandibular symphysis and nasal bone deficiencies can be seen [3]. Abnormal clavicular development is a major feature and can range from complete absence of both clavicles to a small unilateral defect [4]. Usually the middle third is affected, suggesting that the disorder begins before the two ossification centers unite [5]. Though skeletal abnormalities are usually most evident in membranous bones, enchondral bone formation can also be involved with abnormalities of the digits [6] and clivus [7]. The observation that CCD is not a simple malformation syndrome has resulted in the change in designation from a dysostosis to a dysplasia [6]. A mouse model with mutation 320, induced by radiation, has been shown to have skeletal abnormalities very similar to those of CCD [6].

Cases of CCD can occur sporadically but many are inherited, with at least some families exhibiting an autosomal inheritance pattern [8]. An autosomal dominant pattern has also been noted with one-third being new mutations [9]. Linkage studies in families with CCD have mapped the gene for autosomal dominant CCD to the short arm of chromosome 6 [10]. Rearrangement involving chromosome 8 has been described in three unrelated cases, all of whom had additional abnormalities not usually associated with CCD [11]. Our patient had a normal female karyotype with no evidence of that chromosomal abnormality.

Wormian bones are small, irregular bones that are found most often in the region of the lambdoidal sutures. They may be normal variants and are determined genetically in certain populations [12]. They are associated with many congenital abnormalities and syndromes, the four most prominent of which are CCD, osteogenesis imperfecta, congenital hypothyroidism, and hypophosphatasia [13]. In view of the clavicular involvement in the present case, the latter three diagnoses were not seriously considered. One study found that 90% of children with wormian bones had disorders of the central nervous system (CNS), suggesting that wormian bones are markers for CNS abnormalities [14]. CNS problems noted in patients with wormian bones include hydrocephalus, microcephaly, macrocephaly, craniostenosis, cerebral palsy, mental retardation (MR), and convulsive disorders [14].

Though most patients with CCD have normal intelligence and a good prognosis, malformations and/or malfunctions of the CNS have been described. These include hypertonia, MR, hydrocephalus, "atrophy" of the rostral end of the corpus callosum and cingulate gyrus, and syringomyelia [4,15].

Most reported cases are those of adults or children. Descriptions of neonatal cases, particularly lethal ones, are rare and fetal cases have not been reported [2,11,16]. In spite of the severely abnormal skulls, there have been only rare reports of cerebral injury related to birth, including rupture of the superior sagittal sinus [17]. In our case, we assign the mechanism of death to severe in utero central nervous system injury secondary to hemorrhage and hypoxia/ischemia. We base this conclusion on the absence of developmental CNS abnormalities, the clinical findings already present at birth, and the pathological findings indicative of a prolonged process. We can only speculate that the skull abnormality contributed to vulnerability to this catastrophic event or events.

One CCD-related condition, the Yunis-Varon syndrome (YVS), is associated with neurologic findings similar to those in our case. In this condition there can be agenesis of the corpus callosum with dilatation of the occipital horns of the lateral ventricles, hematomas, and/or changes resulting from hypoxia with neuronal loss involving the cerebral cortex, basal ganglia, cerebellar dentate nuclei, medullary olives, and the anterior horns [18]. Patients with YVS additionally display severe micrognathia and abnormalities of the distal extremities [18,19]. Our case does not adequately match the phenotype of YVS. Whether the phenotypic differences of CCD and YVS are related to an identical or to related genetic defects awaits future clarification. Yunis and Varon [20] described a recessively inherited disorder with features not seen in CCD, emphasized specific hand anomalies, and considered the disorder to be an entity separate from CCD. The possibility that this case represents a portion of a spectrum of phenotypic variation ranging from CCD to YVS cannot be excluded at this time.

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