Child's Nerv Syst (1991) 7:21–26

Child's Nervous System CNS

Cerebral abnormalities in thanatophoric dysplasia

Cynthia L. Coulter [1]*, Richard W. Leech [2], Roger A. Brumback [1,2,3,4], and G. Bradley Schaefer [3]

[1] Department of Neurology, [2] Department of Pathology, and [3] Department of Pediatrics, University of Oklahoma College of Medicine, and [4] Veterans Affairs Medical Center, Oklahoma City, Oklahoma, USA

Received April 14, 1990

Abstract. Neuropathologic evaluation of two infants with thanatophoric dysplasia displayed typical gross morphologic characteristics and a distinct pattern of brain malformations, including anomalies of the temporal lobe gyri and hippocampus, neuroglial heterotopias, fiber tract hypoplasia, and dysplasia of deep nuclei. Increased numbers of horizontal cells of Cajal-Retzius were striking in frequency and distribution. The pattern of abnormalities suggests arrest of cerebral cortical ontogeny late in development. As with the mucopolysaccharidoses, a shared common metabolic pathway is a potential mechanism for development of widespread bony and somatic abnormalities and associated central nervous system anomalies.

Key words: Thanatophoric dysplasia – Dwarfism – Chondrodystrophy – Cerebral anomalies

Thanatophoric dysplasia, a rare chondrodystrophic syndrome, was initially reported in 1967 by Maroteaux and co-workers [22], who described the typical morphologic and radiographic findings in four cases and differentiated the syndrome from achondroplasia. Since that original report, a variety of central nervous system abnormalities have been described [3, 7, 10, 13, 14, 16, 23, 27, 32, 33, 37]. Approximately 30 reported cases have included examination of the brain, but central nervous system anomalies have been incompletely documented in many studies. We report two cases with detailed neuropathologic findings (including Golgi study of the cerebellum) and review the current literature.

* *Present address and address for offprint requests:* Department of Neurology, Creighton University Medical Center, 601 North 30th Street, Suite 2342, Omaha, NE 68131, USA

Case presentations

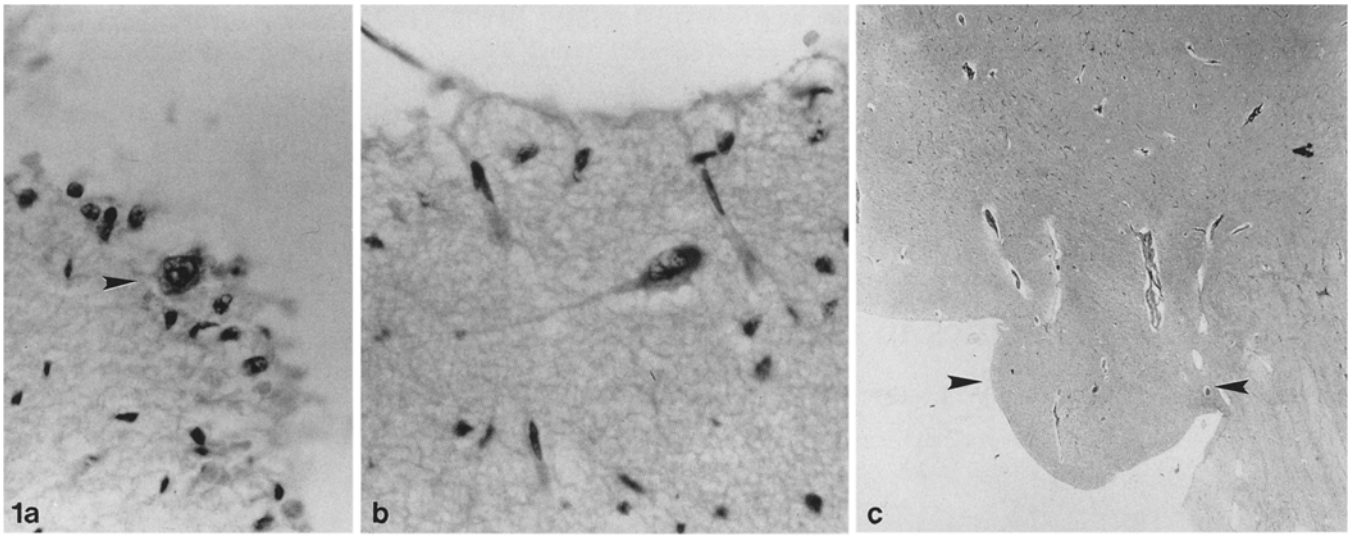
Case 1

This term female infant was delivered to a 27-year-old gravida III, para 2 mother by cesarean section after fetal movement had ceased and ultrasound had revealed multiple skeletal anomalies. The Apgar scores were 1 and 5 at 1 and 5 min, respectively. Immediate intubation was required. Multiple anomalies characteristic of thanatophoric dysplasia were noted, including a large anterior fontanel, flat occiput, flat facies with prominent forehead, flattened nasal bridge with upturned nares, high arched palate, small mandible, small chest, and rhizomelic shortening of all extremities with prominent skinfolds. The palmar and plantar creases were normal. The child weighed 3,725 g and had a fronto-occipital head circumference of 38 cm. The head hair was black and had one right parietal and two left parietal whorls. The hairline was low over the nape of the neck. The neck appeared short with redundant skinfolds. Skeletal radiographs showed findings typical of thanatophoric dysplasia. The infant died less than 24 h after birth.

At autopsy, the chest circumference was 32 cm. The heart had normal chambers and valves, and the ductus arteriosus was widely patent. The lungs were small and hypoplastic. Examination of the ribs and humeri recapitulated the radiologic observations. A nodule of adrenal cortex was found adjacent to one ovary. Sections of the growth zones in the rib, humerus, and vertebrae showed growth arrest lines extending across the zone of provisional ossification. Chondrocytes were evenly spaced, but formed only rudimentary columns. The placenta was meconium stained but otherwise normal. The karyotype was 46XX, normal female.

After formaldehyde fixation, the brain weighed 540 g. External examination of the brain showed that the temporal lobes were enlarged bilaterally. The optic tracts were hypoplastic. On coronal section of the cerebral hemispheres, the thickness of corpus callosum in the midline at the level of the anterior commissure was 2 mm.

Microscopic examination of the temporal lobes showed the hippocampus to be grossly disorganized with poor orientation of the pyramidal cells. The dentate gyrus was absent. Horizontal cells of Cajal-Retzius were scattered haphazardly without orientation throughout the molecular layer of the cortex, singly and in loose groupings (Fig. 1a, b). More rostrally in the temporal lobe there were jumbled nests of pyramidal cells in the presumptive location of the amygdaloid nuclei, which could not otherwise be identified. Large neuroglial heterotopias were found in the subarachnoid space of the temporal lobes, in the molecular layer of the cortex, and the deep white matter of the temporal lobe. In the inferior frontal cortex frequent isolated Cajal-Retzius neurons were found in the molecu-



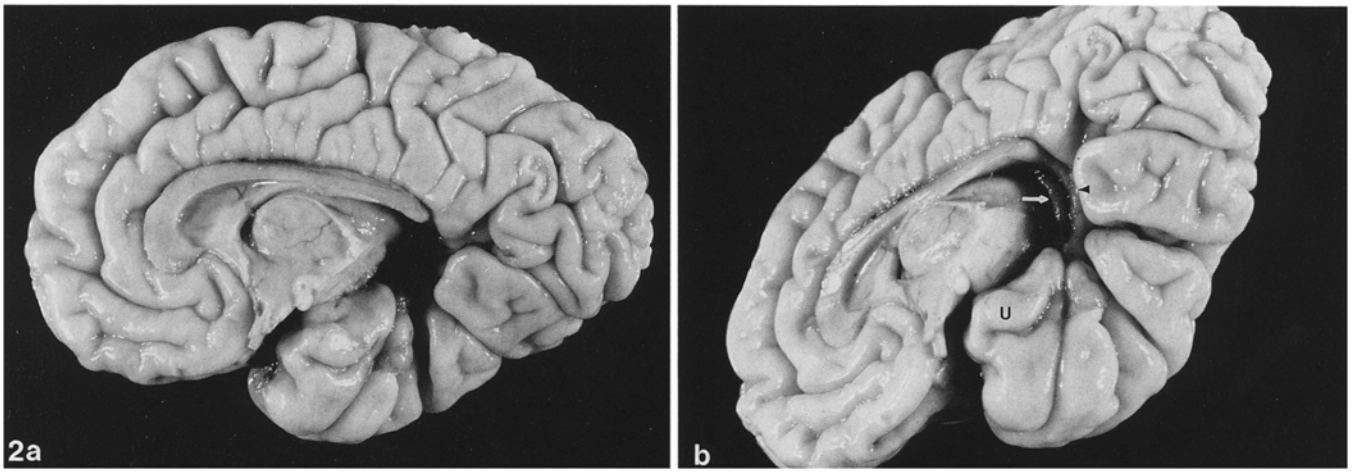


Fig. 1 a–c. Case 1. Horizontal cells (neurons) of Cajal-Retzius at the pial membrane in the inferior temporal cortex (**a**), and in the molecular layer of the cingulate gyrus (**b**). H & E, original magnification, ×400. Coronal section showing hypoplastic optic tract (**c**). LFB-PAS-H, original magnification, ×10

Fig. 2 a, b. Case 2. Medial hemispheric surface showing hypoplastic corpus callosum and temporal gyral abnormalities; note deep sulci oriented at right angles to the long axis of the temporal lobe (**a**). Oblique view of the medial hemispheric surface (**b**) showing fornix (*white arrow*), posteriorly rotated hippocampus (*black arrowhead*), and uncus (*U*)

lar layer. The white matter of the corpus callosum was gliotic. The optic tracts were hypoplastic (Fig. 1 c). The midbrain showed a neuroglial heterotopia in the dorsal lateral region. In the midbrain, the nuclei of the third cranial nerves were poorly organized, fused, and failed to form two discrete nuclei. In the cerebellum a few large heterotopic Purkinje cells were located near the roof of the IV ventricle. The medullary pyramids were small. The spinal cord appeared normal.

Case 2

This patient was a 36-week-gestation male infant born to a 27-year-old gravida I, para 1, woman following spontaneous rupture of the membranes. The Apgar scores were 4 and 6 at 1 and 5 minutes, respectively. Transferred to the Children's Hospital of Oklahoma at the age of 6 h because of respiratory distress, his weight was 2 230 g, length 38 cm, and fronto-occipital head circumference 36.5 cm. Dysmorphic features were identical to those seen in case 1. A radiographic skeletal survey showed marked bowing of the limbs with metaphyseal flaring, platyspondyly with narrowed interpedicular distances, square shape of the iliac crest and scapula, a short cranial base, and short ribs with flared ends. He died at the age of 3 days.

At autopsy, the thorax was 23 cm in circumference at the level of the nipples. The testes were located within the inguinal canals. The lungs were severely hypoplastic; the heart appeared normal. The posterior fossa was shallow. Karyotype was 46XY, normal male; the placenta showed moderate ischemic changes.

The brain weighed 502 g. The cerebellum was small. The temporal lobes were enlarged bilaterally. The gyral pattern on the inferior surface of the temporal lobe was abnormal (Fig. 2 a, b). There were three deep sulci perpendicular to the long axis of the temporal lobe and the usual named gyri were difficult to identify. The hippocampus was rudimentary and found only in the most extreme posteromedial portion of the temporal lobe. The splenium of the corpus callosum was hypoplastic.

One hemisphere was cut in serial step sections from the occipital pole to the tip of the temporal lobe. Within the calcarine cortex there were large neurons of Cajal-Retzius present in the outer molecular layer both singly and in groups. There were a few small nodules of heterotopic neurons in the molecular layer (Fig. 3 a), as well as smaller neuroglial nodules in the deep white matter. Polymicrogyria was present in the sulcal depths of the posteromedial tem-

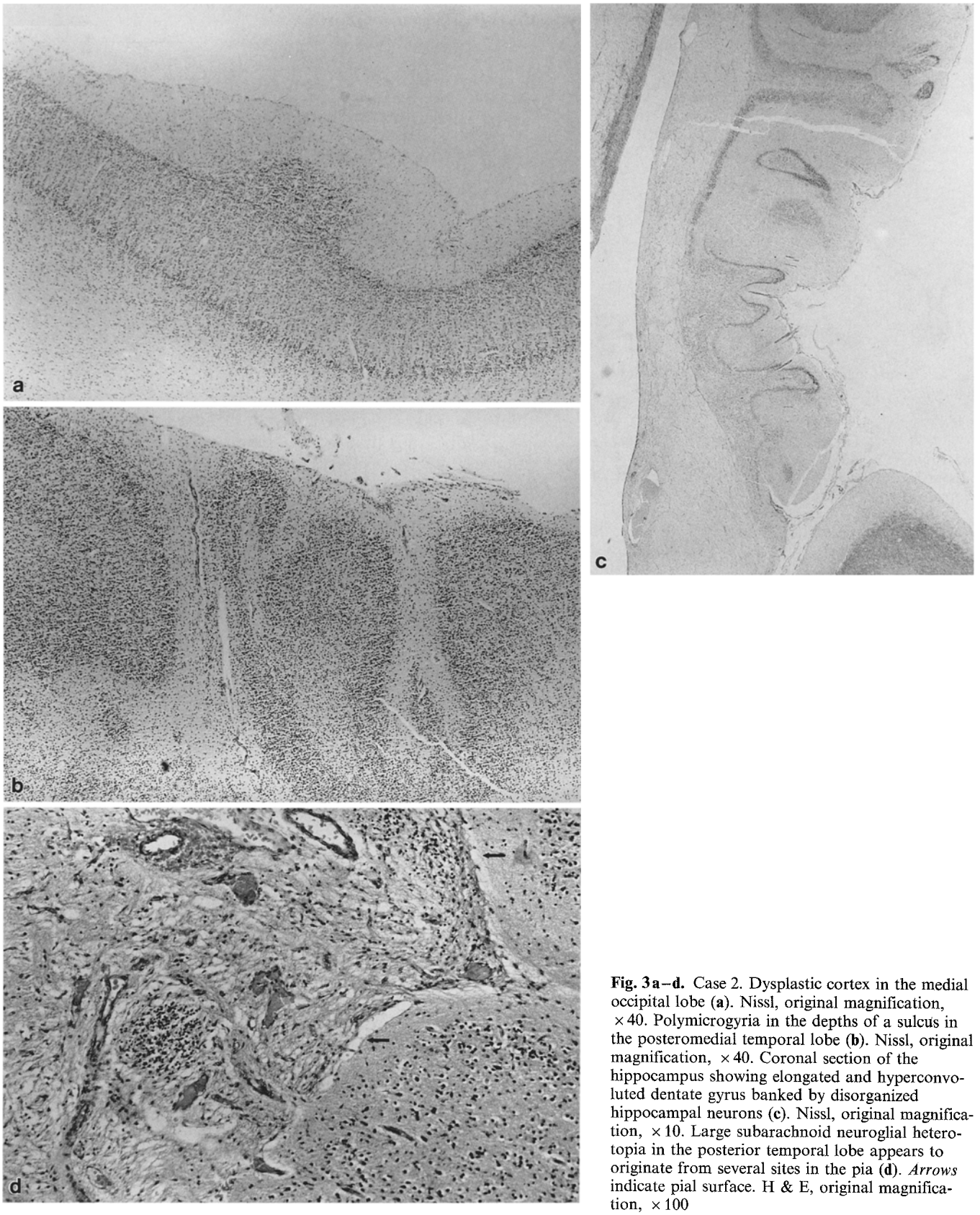


Fig. 3a–d. Case 2. Dysplastic cortex in the medial occipital lobe (**a**). Nissl, original magnification, ×40. Polymicrogyria in the depths of a sulcus in the posteromedial temporal lobe (**b**). Nissl, original magnification, ×40. Coronal section of the hippocampus showing elongated and hyperconvoluted dentate gyrus banked by disorganized hippocampal neurons (**c**). Nissl, original magnification, ×10. Large subarachnoid neuroglial heterotopia in the posterior temporal lobe appears to originate from several sites in the pia (**d**). *Arrows* indicate pial surface. H & E, original magnification, ×100

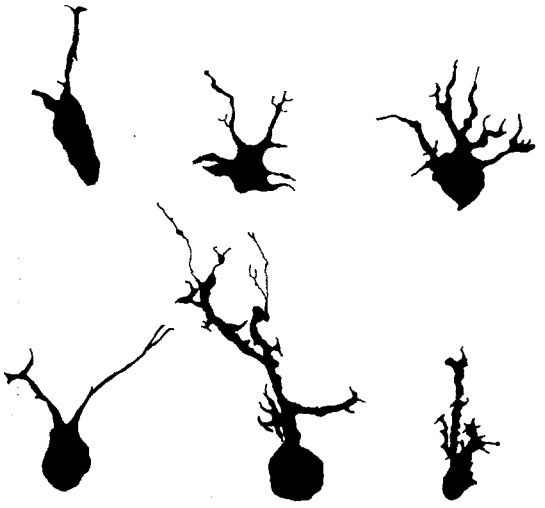


Fig. 4. Camera lucida drawing of Purkinje cells showing the abnormal dendritic branching. Denn Rapid Golgi stain

poral lobe (Fig. 3b). A large cluster of heterotopic neurons was present in the deep white matter near the trigone of the lateral ventricle.

At the junction of occipital and temporal lobes, the normal six-layered cortex became a more poorly organized cortex with a simplified laminar pattern. In the rudimentary, vertically oriented hippocampus, jumbled nests of hippocampal pyramidal neurons were seen, intermixed with scattered clusters of smaller granular neurons. In several sections, the granular cells formed an elongated and hyperconvoluted dentate gyrus banked by poorly organized hippocampal pyramidal neurons (Fig. 3c), with looping swirls of hippocampal neurons intermixed with nests of granular cells within the ascending portion of the hippocampus. In the inferomedial portion of the temporal lobe, neuroglial subarachnoid heterotopias were seen, at times bridging adjacent gyri (Fig. 3d). The cortex in this region was grossly disorganized, whereas further laterally and superiorly in the temporal lobe, the cortex had a more normal laminar pattern. The amygdaloid nucleus could be identified and appeared normal. Occasional nodules of heterotopic neurons were found in the deep white matter of the temporal lobe. An unusual ependymal-lined eventration extending from the ventricular surface was found in the roof of the temporal horn of the lateral ventricle. Variably oriented Cajal-Retzius cells were occasionally identified in the molecular layer of all regions of the cortex, but were most common in the parieto-occipital regions. The thalamus showed abnormal nodular collections of small nuclei that appeared to be glial cells. The basal ganglia contained abnormal bundles of white matter. The inferior olives were normal, and the medullary pyramids were small. In the cerebellum, heterotopic nests of Purkinje cells were found near the dentate nucleus.

Golgi stains [5] of the cerebellum were performed on both cases, with similar findings. Although the majority of Purkinje cells were normal, many Purkinje cells showed bizarre dendritic branches singly and in small groups (Fig. 4).

Discussion

Many early reports of thanatophoric dysplasia provide insufficient details to determine the number and relative frequency of the various central nervous system anomalies [3, 10, 16, 23, 27, 32]. Table 1 is a compilation of the findings of the cases reported thus far. Temporal lobe gyral abnormalities seem to be the most frequently reported anomaly. Typically the temporal lobes are symmetrically enlarged, with broad flat gyri. The sulci are very deep and characteristically aligned perpendicularly or diagonally in relation to the long axis of the temporal lobe, such that the usual temporal gyri cannot be identified with certainty. Abnormalities of the organization of the hippocampal formation and dentate gyrus appear equally commonly, although an exact frequency cannot be determined. Megalencephaly, present in about 80% of cases, is the second-most common abnormality. Next in frequency is the presence of neuroglial subarachnoid heterotopias, most commonly in the inferior and medial regions of the temporal lobe and typically within sulci. Posterior fossa hypoplasia has been reported in 45% of cases and may be associated with cerebellar and brainstem hypoplasia, although this concordance has not been well documented. About half the cases have had mildly to severely dilated ventricles. In some cases this dilation apparently primarily involved the temporal horns of the lateral ventricles. Hypoplasia of fiber tracts often involves the brainstem corticospinal tracts and the corpus callosum.

Table 1. Neuropathologic findings in 29 cases of thanatophoric dysplasia

	No.
Clover leaf skull	7/29
Posterior fossa hypoplasia	13/29
Megalencephaly	23/29
Ventricular dilation	14/29
Temporal lobe gyral abnormality	24/29
Subarachnoid heterotopia	19/29
Corpus callosum hypoplasia	7/29
Dentate nucleus dysplasia	8/29
Inferior olive dysplasia	7/29
Other nuclear dysplasia	8/29
Fiber tract abnormality	14/29

Our two cases had the typical phenotypic features of thanatophoric dysplasia, which is one of several forms of lethal chondrodystrophy [17, 24, 26, 30, 34].

Two recent series [13, 37] have confirmed previous findings and emphasized abnormalities of the hippocampus and brainstem, including a dysplastic or absent dentate gyrus, failure of development of Ammon's horn, neuroglial heterotopias in the temporal lobe, the subependymal region, deep white matter, cortex, or in the subarachnoid space. Many large pyramidal neurons were seen in the molecular layer of the cortex, especially in the temporal lobes [13]. Dysplasia of brainstem and cerebellar nuclear groups was frequent but variable: a hyperconvoluted dentate nucleus was most common. Abnormalities also occurred in the inferior olive, basal ganglia, caudate nucleus, thalamus, and lateral geniculate. Fiber tract hypoplasia commonly involved the internal capsule, temporopontine and corticospinal fibers in the midbrain and pons, and the medullary pyramids. Purkinje cell heterotopias were noted in the cerebellar white matter. Golgi studies in one case [33] showed immature cortical neurons with short dendrites. Purkinje cells had small, poorly branching dendritic trees.

Table 2. Neuropathologic abnormalities in chondrodystrophic syndromes

Syndrome	Neuropathologic findings
Achondroplasia	Megalencephaly, hydrocephalus
Ellis-van Creveld	Heterotopic gray matter, gyral anomalies, cerebellar vermal atrophy, absence or thinning of corpus callosum, hydrocephalus
Campomelic syndrome	Megalencephaly, abnormal cortex, thalamus, caudate; absent or hypoplastic olfactory tract or bulb, hydrocephalus
Short rib polydactyly syndrome (type II)	Pachygyria, hypoplastic cerebellar vermis, absent olfactory bulbs, midbrain and aqueductal malformation, Dandy-Walker malformation
Rhizomelic chondrodysplasia punctata	Heterotopic gray matter, Dandy-Walker malformation, dysplastic dentate nucleus, hydrocephalus
Thanatophoric dysplasia	Megalencephaly, temporal lobe gyral anomalies, subarachnoid heterotopia, brainstem and cerebellar nuclear dysplasia, fiber tract abnormalities

It is sometimes difficult to distinguish intrinsic central nervous system dysmorphism from the effects of deformational forces. Table 2 shows the chondrodysplasias in which central nervous system anomalies have been reported. For the most part, the exact incidence of the specific abnormalities in each syndrome is unknown.

Megalencephaly and hydrocephalus are sometimes seen in achondroplasia [6], although the brain appears otherwise unremarkable and intelligence is usually normal. Heterotopic gray matter, gyral abnormalities, vermal atrophy, and thining of the corpus callosum have been found in the Ellis-Van Creveld syndrome [2, 29], but most of these patients are of average intellect. The other chondrodysplasias are often fatal in the neonatal period and show an increased incidence of brain anomalies. In the campomelic syndrome, about half of the brains studied showed a lack of olfactory bulbs or tracts [1, 11, 15, 25, 31]. Pachygyria, vermal hypoplasia, absent olfactory bulbs, midbrain and aqueductal malformations, and Dandy-Walker malformation have been described in some cases of the short rib-polydactyly syndrome type II (Majewski type) [4, 20]. Rhizomelic chondrodysplasia punctata, recently found to be a disorder of peroxisomal function resulting in decreased plasmalogen synthesis [12], has been associated with heterotopic gray matter, the Dandy-Walker malformation, dysplastic dentate nuclei, and ventricular dilation [35].

The pattern of central nervous system dysmorphism seen in infants with thanatophoric dysplasia appears to be a specific and integral component of the syndrome, and not the result of deformational factors. Although microgyria and abnormalities of the posterior and middle cranial fossae contents have previously been ascribed to ischemia or hypoperfusion resulting from morphological abnormalities at the base of the skull, such a hypothesis would not account for more widespread disturbances of cortical development and neuronal migration. In addition, Knisely and co-workers [18] have found typical brain changes in a 19-week fetus. The temporal lobe structures affected form at or before 14.5 weeks, prior to the time that bony deformities could produce changes, suggesting a developmental rather than deformational factor operating early in maturation. A disturbance of intermediary metabolism could possibly account for the disrupted nervous system development. Similar changes have been reported in known metabolic disorders. Disordered neuronal migration with gray matter heterotopia, polymicrogyria, dysplastic inferior olivary nucleus, and abnormal cerebellar Purkinje cells have been observed in Zellweger syndrome [8, 28 36] which, like rhizomelic chondrodysplasia punctata, has a deficiency of peroxisomal function [9]. Unfortunately, investigation of peroxisomal function has not yet been undertaken in thanatophoric dysplasia, although an abnormality of proteoglycan intracellular transit in fibroblasts has been identified [19]. It is unknown whether such an abnormality could be causally linked to anomalies of brain development.

Of particular interest is the increased number of horizontal cells of Cajal-Retzius in the molecular layer of the cortex, especially in the temporal lobe. Embryologically, these cells are among the first neurons to differentiate, and subsequent waves of maturing neurons synapse with and orient in relation to these Cajal-Retzius cells [21]. A disturbance in the early proliferation or function of these cells could contribute to later abnormal neuronal migration and hence disorganization or abnormal cortical development, including subarachnoid heterotopias and gyral malformations. Detailed studies of cortical cytoarchitecture, especially in the earlier fetal periods, may yield additional information concerning the process of both abnormal and normal brain development. Furthermore, investigation of a possible metabolic disorder in thanatophoric dysplasia may reveal a common biochemical explanation for the changes in both bone and brain.

References

1. Austin GE, Gold RH, Mirra JM, Perry S, Moedjono S (1980) Long-limbed campomelic dwarfism: a radiologic and pathologic study. Am J Dis Child 134:1035–1042
2. Blackburn MG, Belliveau RE (1971) Ellis-van Creveld syndrome: a report of previously undescribed anomalies in two siblings. Am J Dis Child 122:267–270
3. Bloomfield JA (1970) Cloverleaf skull and thanatophoric dwarfism. Australas Radiol 14:429–434
4. Chen H, Yang SS, Gonzales E, Fowler M, Al Saadi A (1980) Short-rib polydactyly syndrome, Majewski type. Am J Med Genet 7:215–222
5. Denn AC (1981) The Denn-Golgi stain – a modified Defano's silver impregnation stain for dendritic spines and neurofibrils. J Histotech 4:127–128
6. Dennis JP, Rosenberg HS, Alvord EC (1961) Megalencephaly, internal hydrocephalus and other neurological aspects of achondroplasia. Brain 84:427–445
7. Galatioto S, Gemelli M, Granese D, Longo M (1984) Thanatophoric dwarfism and "cloverleaf skull" syndrome: a neuropathological report. Pathologica 76:255–261
8. Giustina ED, Goffinet AM, Landrieu P (1981) A Golgi study of the brain malformation in Zellweger's cerebro-hepato-renal disease. Acta Neuropathol (Berl) 55:23–28

9. Goldfischer S, Moore CL, Johnson AB, et al (1973) Peroxisomal and mitochondrial defects in the cerebro-hepato-renal syndrome. Science 182:62–64
10. Goutières F, Aicardi J, Farkas-Bargeton E (1971) Une malformation cérébrale particulière associée au nanisme thanatophore. Rev Neurol (Paris) 25:435–440
11. Hall BD, Spranger JW (1980) Campomelic dysplasia: further evaluation of a distinct entity. Am J Dis Child 134:285–289
12. Heymans HSA, Dorthuys JWE, Nelck G, Wanders RJA, Schutgens RBH (1985) Rhizomelic chondrodysplasia punctata: another peroxisomal disorder. N Engl J Med 313:187–188
13. Ho KL, Changa CH, Yang SS, Chason JL (1984) Neuropathologic findings in thanatophoric dysplasia. Acta Neuropathol (Berl) 63:218–228
14. Hori A, Friede RL, Fischer G (1983) Ventricular diverticles with localized dysgenesis of the temporal lobe in cloverleaf skull anomaly. Acta Neuropathol (Berl) 60:132–136
15. Houston CS, Opitz JM, Spranger JW, et al (1983) The campomelic syndrome: review, report of 17 cases, and follow-up on the currently 17-year-old boy first reported by Maroteaux et al in 1971. Am J Med Genet 15:3–28
16. Huguenin M, Godard C, Ferrier PE, Bamatter F (1969) Two different mutations within the same sibship: thanatophoric dwarfism and Ullrich-Feichtiger syndrome. Helv Paediatr Acta 24:239–245
17. Jones KL (1988) Smith's recognizable patterns of human malformation. Saunders, Philadelphia, pp 290–291
18. Knisely AS, Ambler MW (1989) Temporal lobe abnormalities in thanatophoric dysplasia. Pediatr Neurosci 14:169–177
19. Knisely AS, Reeder JW, Ivatt R (1989) Intracytoplasmic retention of chemically normal proteoglycans characterizes cultured fibroblastic-line cells from infants with thanatophoric dysplasia (abstract). Lab Invest 60:48
20. Kuchelmeister VK, Garcia H (1988) Schwere zerebrale Mißbildungen bei atypischem Short-Rib-Polydactyly-Syndrom (SRP-S). Zentralbl Allg Pathol 34:561–566
21. Marin-Padilla M (1988) Early ontogenesis of the human cerebral cortex. In: Peters A, Jones EG (eds) Cerebral cortex, vol 7. Development and maturation of cerebral cortex. Plenum Press, New York, pp 1–35
22. Maroteaux P, Lamy M, Robert JM (1967) Le nanisme thanatophore. Presse Med 75:2519–2524
23. Martinelli B, Campailla E, Ferrari G (1975) Malformation cérébrale particulière et nanisme thanatophore. Arch Fr Pediatr 32:455–460
24. McKusick VA (1986) Mendelian inheritance in man, 7th edn. Johns Hopkins University Press, Baltimore, pp 710–711
25. Moedjono SJ, Crandall BF, Sparkes RS, Feldman GM, Austin GE, Perry S (1980) The campomelic syndrome in singleton and monozygotic twins. Clin Genet 18:397–401
26. Moir DH, Kozlowski K (1976) Long survival in thanatophoric dwarfism. Pediatr Radiol 5:123–125
27. Partington MW, Gonzales-Crussi F, Khakee SG, Wollin DG (1971) Cloverleaf skull and thanatophoric dwarfism: report of four cases, two in the same sibship. Arch Dis Child 46:656–664
28. Powers JM, Tummons RC, Caviness VS, Moser AB, Moser H (1989) Structural and chemical alterations in the cerebral maldevelopment of fetal cerebro-hepato-renal (Zellweger) syndrome. J Neuropathol Exp Neurol 48:270–289
29. Rosenberg S, Carneiro PC, Zerbini MCN, Gonzales CH (1983) Chondroectodermal dysplasia (Ellis-van Creveld) with anomalies of CNS and urinary tract. Am J Med Genet 15:291–295
30. Saldino RM (1973) Radiographic diagnosis of neonatal short-limbed dwarfism. Med Radiogr Photogr 49:61–95
31. Schmickel RD, Heidelberger KP, Poznanski AK (1973) The campomelique syndrome. J Pediatr 82:299–302
32. Shah K, Astley R, Cameron AH (1973) Thanatophoric dwarfism. J Med Genet 10:243–252
33. Shigematsu H, Takashima S, Otani K, Ieshima A (1985) Neuropathology and Golgi study on a case of thanatophotoric dysplasia. Brain Dev 7:628–631
34. Sillence DO, Rimoin DL, Lachman RS (1978) Neonatal dwarfism. Pediatr Clin North Am 25:453–483
35. Tasker WG, Mastri AR, Gold AP (1970) Chondrodystrophica calcificans congenita (dysplasia epiphysalis punctata): recognition of the clinical picture. Am J Dis Child 119:122–127
36. Volpe JJ, Adams RD (1972) Cerebro-hepato-renal syndrome of Zellweger: an inherited disorder of neuronal migration. Acta Neuropathol (Berl) 20:175–198
37. Wongmongkolrit T, Bush M, Roessmann U (1983) Neuropathological findings in thanatophoric dysplasia. Arch Pathol Lab Med 107:132–135