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Review article

Infantile tauopathies: Hemimegalencephaly; tuberous sclerosis complex; focal cortical dysplasia 2; ganglioglioma ☆

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Abstract

Tau is a normal microtubule-associated protein; mutations to phosphorylated or acetylated forms are neurotoxic. In many dementias of adult life tauopathies cause neuronal degeneration. Four developmental disorders of the fetal and infant brain are presented, each of which exhibits up-regulation of tau. Microtubules are cytoskeletal structures that provide the strands of mitotic spindles and specify cellular polarity, growth, lineage, differentiation, migration and axonal transport of molecules. Phosphorylated tau is abnormal in immature as in mature neurons. Several malformations are demonstrated in which upregulated tau may be important in pathogenesis. All produce highly epileptogenic cortical foci. The prototype infantile tauopathy is (1) hemimegalencephaly (HME); normal tau is degraded by a mutant *AKT3* or *AKT1* gene as the aetiology of focal somatic mosaicism in the periventricular neuroepithelium. HME may be isolated or associated with neurocutaneous syndromes, particularly epidermal naevus syndromes, also due to somatic mutations. Other tauopathies of early life include: (2) tuberous sclerosis complex; (3) focal cortical dysplasia type 2b (FCD2b); and (4) ganglioglioma, a tumor with dysplastic neurons and neoplastic glial cells. Pathological tau in these infantile cases alters cellular growth and architecture, synaptic function and tissue organization, but does not cause neuronal loss. All infantile tauopathies are defined neuropathologically as a tetrad of (1) dysmorphic and megalocytic neurons; (2) activation of the mTOR signaling pathway; (3) post-zygotic somatic mosaicism; and (4) upregulation of phosphorylated tau. HME and FCD2b may be the same disorder with different timing of the somatic mutation in the mitotic cycles of the neuroepithelium. HME and FCD2b may be the same disorder with different timing of the somatic mutation in the mitotic cycles of the neuroepithelium. Tauopathies must be considered in infantile neurological disease and no longer restricted to adult dementias. The mTOR inhibitor everolimus, already demonstrated to be effective in TSC, also may be a potential treatment in other infantile tauopathies.

Keywords: Infantile tauopathies; Hemimegalencephaly; Tuberous sclerosis complex; Focal cortical dysplasia type 2; Ganglioglioma; Epidermal naevus syndromes; Proteus syndrome; mTOR pathway; Postzygotic somatic mosaicism; Epilepsy; Everolimus

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1. Introduction

Tauopathies are a designated group of adult neurodegenerative diseases characterized by dementia and neuronal degeneration, accompanied by the overexpression of a pathologically phosphorylated or, less frequently, an acetylated form of the microtubule-associated protein tau [1,2]. Examples include frontotemporal lobar degeneration, Alzheimer disease, Pick disease and a form of Parkinson disease with dementia. Until recently, tauopathies were unknown in infants and children. Several neurological conditions of early life are now documented with upregulation of abnormally phosphorylated tau. The filamentous ultrastructure of neurofilaments is not identical to adult dementias, hence should not be considered as traditional tauopathies. In part it is a semantic question as concepts and terms evolve over time, sometimes becoming broader and sometimes narrower in definition. Several neurological disorders of early life are now documented that we would regard as developmental "infantile tauopathies". The detection of phosphorylated tau in brain tissue of human fetuses, infants and children helps to explain the pathogenesis and even suggests potential therapeutic approaches, in addition to seizure control.

1.1. Hemimegalencephaly (HME)

This hamartomatous malformation involving only one cerebral hemisphere, with or without ipsilateral brainstem and cerebellar involvement is well characterized clinically, by neuroimaging and neuropathologically [3–7]. Severe infantile epilepsy is a common complication, often beginning in the neonatal period or early infancy. HME may be isolated or be associated with neurocutaneous syndromes, notably the epidermal nevus syndromes and especially linear sebaceous nevus syndrome, keratinocytic nevus syndrome and Proteus syndrome [8–11]. The genetic defect is a mutation of the *AKT1* gene in Proteus syndrome [12] and *AKT3* in isolated HME not associated with Proteus syndrome [13,14]. The pathogenesis of the disturbance in cellular differentiation, lineage, maturation and migration are due to a focal post-zygotic somatic mutation involving undifferentiated neuroepithelial cells of the periventricular region [13–16].

Based on the theoretical premise that in these conditions the cytological disturbance must occur very early in the maturation of neuroepithelial cells, a microtubular disorder was suspected because microtubules are important components of the early cytoskeleton and determine neuronal polarity, morphology, growth and differentiation including neurotransmitter synthesis and synaptogenesis. Either paucity or excess of tau can retard neurogenesis and neuronal differentiation; other microtubule-associated proteins can compensate for loss only to a limited extent [17]. MAPs include many of those involved in neuroblast migration (e.g. *DCX*, *ARX*, *LIS1*); tau protein is another of these MAPs. For this reason, we applied immunocytochemical antibodies against the abnormal phosphorylated tau protein commonly expressed in adult tauopathies to resected brain tissue as a surgical attempt to control epilepsy, to 3 infants with HME. One of our cases was diagnosed prenatally by fetal MRI and later shown to have Proteus syndrome [18]. Another was diagnosed at birth because of refractory epilepsy beginning on post-natal day 1, and died of postoperative complications a few hours after resection at age 2½ months; autopsy was performed within 12 h after death and enabled a comparison of the HME with the apparently normal contralateral hemisphere and with subcortical structures of the brain. We found a strong expression of phosphorylated tau in the dysplastic, hamartomatous tissue of HME in the cerebral cortex and hippocampus (Fig. 1A–E). The non-HME hemisphere of the infant who died showed only rare scattered dysmorphic neurons expressing tau and strong reactivity limited to the cingulate gyrus [18]. The reason for the selective involvement of this gyrus is uncertain, but the anterior cingulate gyrus also is selectively vulnerable in other hereditary and sporadic tauopathies in adult dementias [19]. Examination of the mTOR pathway in 2 of our 3 cases (performed by Dr. Peter B. Crino, University of Pennsylvania) additionally showed strong activation, similar to that of tuberous sclerosis complex [18]. We now have another case in a male child 9 years of age with HME whose temporal and frontal neocortical resection for epilepsy also exhibits focal tau over-expression (Fig. 1F). As with tuberous sclerosis (see below), everolimus might be beneficial to reduce the cerebral overgrowth in HME [18].

1.2. Tuberous sclerosis complex (TSC)

This autosomal dominant disease due to mutation in one of two genes, TSC1 or TSC2, at loci 9q34 and 16p13.3 respectively, is the best studied prototype hamartomatous malformation [20–23]. They encode the proteins hamartin and tuberin that interact as complexes: tuberin is a cytosolic chaperone for hamartin [24]. These gene products are expressed in cortical tubers, but are immunoreactive in normal neurons as well as dysmorphic cells, of both neuronal and glial lineage, and also balloon cells [25,26]. Cortical tubers begin forming prenatally and are demonstrated histopathologically in midgestational fetal and term neonatal brains [27–29]. The mTOR pathway is abnormally activated and has led to treatment using everolimus, a rapamycin analog and mTOR inhibitor, which results in regression of subependymal giant cell astrocytomas. A corresponding decrease in size of cortical tubers is not as prominent, but facial dermal fibroangiomata may