Abstract

Granular/fuzzy astrocytes (GFAs), a subtype of 'aging-related tau astrogliopathy', are noted in cases bearing various neurodegenerative diseases. However, the pathogenic significance of GFAs remains unclear. We immunohistochemically examined the frontal cortex, caudate nucleus, putamen, and amygdala in 105 cases composed of argyrophilic grain disease cases (AGD, N=26), and progressive supranuclear palsy (PSP, N=10), Alzheimer's disease (AD, N=20), and primary age-related tauopathy cases (PART, N=18) lacking AGD, as well as 31 cases bearing other various neurodegenerative diseases to clarify (i) the distribution patterns of GFAs in AGD, and PSP, AD, and PART lacking AGD, (ii) the impacts of major pathological factors and age on GFA formation, and (iii) immunohistochemical features useful to understand the formation process of GFAs. In AGD cases, GFAs consistently occurred in the amygdala (100%), followed by the putamen (69.2%), and caudate nucleus and frontal cortex (57.7%, respectively). In PSP cases without AGD, GFAs had developed in almost all regions examined. In AD cases without AGD, GFAs were less frequent, developing preferably in the putamen (35.0%) and caudate nucleus (30.0%). PART cases without AGD had GFAs most frequently in the amygdala (35.3%), being more similar to AGD than to AD cases. Ordered logistic regression analyses using all cases demonstrated that the strongest independent factor of GFA formation in the frontal cortex and striatum was the diagnosis of PSP, while that in the amygdala was AGD. The age was not significantly associated with GFA formation in any region. In GFAs in AGD cases, phosphorylation and conformational change of tau, Gallyas-positive glial threads indistinguishable from those in tufted astrocytes, and the activation of autophagy occurred sequentially. Given these findings, AGD, PSP, AD, and PART cases may show distinct distributions of GFAs, which may provide clues to predict the underlying processes of primary tauopathies.