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Abstract: We report the first detailed examination of the brain of a patient with Wolcott-Rallison syndrome. Wolcott-Rallison syndrome is an extremely rare clinical manifestation of a lack of protein kinase R-like endoplasmic reticulum kinase (PERK) function caused by mutations in the PERK gene EIF2AK3. Protein kinase R-like endoplasmic reticulum kinase is thought to play a significant pathogenetic role in several neurodegenerative diseases, including Alzheimer disease, other tauopathies, and Parkinson disease. The brain of a male patient aged 4 years 7 months showed pathologic and immunohistochemical evidence that the absence of PERK for several years is sufficient to induce early changes reminiscent of various neurodegenerative conditions. These include neurofibrillary tangles (as in progressive supranuclear palsy), FUS-immunopositive and p62-immunopositive neurons, and reactive glial changes. We also detected an increased amount of p62-positive puncta coimmunostaining for LC3 and ubiquitin, suggesting changes in autophagic flux. Studying a human brain with absent PERK function presents the opportunity to assess the long-term consequences of nonfunctioning of PERK in the presence of all of the compensatory mechanisms that are normally active in a living human, thereby confirming the importance of PERK for autophagy in the brain and for
neurodegeneration.