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Contacts with endoplasmic reticulum (ER) tubules mediate endosomal tubule fission events, but the mechanisms underlying this process and consequences of its failure are unclear. Here we show that interaction between an endosomal protein and an ER-localized form of the microtubule severing enzyme spastin drives ER-associated endosomal tubule fission. The functional consequences of this failure of endosomal tubule fission are presented, including in neurons from a knock-in mouse model expressing inactive spastin and human stem cell-derived neurons from a patient with a spastin mutation. Consistent with a role for ER tubules in influencing endosomal tubule fission, we saw similar abnormalities in neurons from mice lacking the ER morphogen REEP1. As mutations in the spastin and REEP1 genes cause axonal degeneration in hereditary spastic paraplegia (HSP), our results implicate failure of an ER-endosome contact process in axonopathy. Furthermore, our observations link many classes of HSP proteins previously considered functionally distinct, in a unifying pathway of HSP pathogenesis.