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COMMENTS TO AUTHORS

This review aims to summarize and critically discuss the use of adeno-associated virus (AAV) in gene therapy of neurodegenerative disorders. It is constructed following a classical scheme providing the summary of main studies and observations for each illness (starting from AD and Parkinson disease and the moving to rare forms of neurodegeneration with subcortical damage such as Huntington disease, ALS, SMA and finally the metabolic Canavan disease). The choice of the studies is correct and presentation (although quite conventional) is well balanced. The authors avoid overstatements in such difficult issue that induced hopes but mostly disappointments.

What is critically missing here is a more general discussion on the meaning of such therapies in diffuse neurological disorders (see the excellent work of Honig in JAMA 2018 questioning the benefits of gene therapy in Alzheimer disease). A comparison with other gene therapies is also warranted. For instance, the use of polymeric nanosystems to deliver target proteins has been intensively discussed (see Bangde et al., Cur Gene Ther 2017 ;17). It is also the case for gene therapy on ER stress signalling (see Gerakis and Hetz FEBS J 2018 ;285). Without a broader view, it is difficult to avoid the impression of an exhaustive list of positive and negative contributions without a take home message. In this respect, Conclusions should be rewritten to provide the authors position about the use, misuse and limitations of gene therapy (with or without adenovirus) in chronic neuropsychiatric disorders. In particular the idea of combined gene therapy (targeting decreased tau, neuronal growth factors and neuroinflammation in AD) should be also taken into account.