Mutant superoxide dismutase aggregates from human ALS spinal cord transmit templated aggregation and fatal ALS disease in mice

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Mutations in superoxide dismutase-1 (SOD1) are a common known cause of amyotrophic lateral sclerosis (ALS). ALS patients and transgenic model mice carrying mutant human SOD1 (hSOD1) develop aggregates of the protein in motor neurons. In transgenic mice two strains of aggregates (denoted A and B) can arise. Inoculation of minute amounts of A or B aggregates into spinal cords of asymptomatic hSOD1 transgenic mice initiated spreading, exponentially growing templated hSOD1 aggregations concomitantly with premature fatal ALS. Here we explored whether prion-competent mutant hSOD1 aggregates also exist in human ALS. Aggregate seeds were prepared from spinal cords from a patient and transgenic mice carrying the hSOD1G127Gfs*7 mutation by centrifugation through density cushions. G127Gfs*7 mutant hSOD1 has a 26 amino acids long C-terminal truncation, but the core structure of the aggregates was strain A-like. Inoculation of the seeds into lumbar spinal cord of hSOD1-expressing mice induced strain A hSOD1 aggregation propagating along the neuraxis and fulminant fatal ALS. The potencies of the human-derived seed preparations were high and disease was initiated under conditions plausible to exist in human motor areas. Human and murine control seeds had no effect. Our results suggest that prion-like templated spread of hSOD1 aggregation could be the primary pathogenic mechanism, not only in hSOD1 transgenic models, but also in hSOD1-induced ALS in man.