Neurofilaments and tau in CSF in an infant with SMA type 1 treated with nusinersen

Spinal muscular atrophy (SMA) is a monogenetic motoneuron disease with onset in childhood or adolescence, clinically characterised by spinal and bulbar muscle weakness and atrophy. SMA type 1 is the acute and thus most severe form of disease, where an early and progressive loss of motoneurons occurs. Recently, the antisense-oligonucleotide nusinersen has been approved for treatment. Nusinersen has to be administered intrathecally by lumbar puncture on days 0, 14, 28 and 63 followed by maintenance therapy at intervals of 4 months. Clinical studies showed an improvement in motor function, particularly in patients with SMA type 1.[1]

Neurofilaments (Nf) are important structural elements of neurons and their axons.[2] In various neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS), increased cerebrospinal fluid (CSF) levels of Nf were observed and their usefulness for diagnosis and prognosis was demonstrated.[3] Increased CSF tau levels have been found in several neurological diseases associated with significant neuronal loss; however, it still remains a matter of debate whether CSF tau can serve as diagnostic marker in ALS.[4 5]

Therefore, the question arises, what role CSF Nf and tau play in SMA and how important the use of these parameters in SMA could be with regard to new therapies. In this letter, we describe neurofilament light chain (NfL) and phosphorylated neurofilament heavy chain (pNfH) along with total tau (ttau) and phosphorylated tau (ptau) in CSF in an SMA type 1 infant treated with nusinersen. First symptoms of muscular hypotonia were recognised by the parents at the age of 4 months. Homozygous deletion in the *SMN1* gene and two *SMN2* copy numbers were confirmed by molecular genetic analysis. At the age of 8 months, therapy with nusinersen was initiated (early access programme). At this time, the girl was not able to sit unassisted, head control was impaired and above all, she was severely affected bulbar and showed signs of respiratory insufficiency. Only 2 months after the first dose, clinical examination revealed a significant improvement in motor function. After 6 months of therapy, at the age of 14 months, the girl was able to sit unassisted. At the age of 20 months, the girl was able to stand and walk some steps with little assistance, respiratory function was stable, but bulbar affection still very prominent.

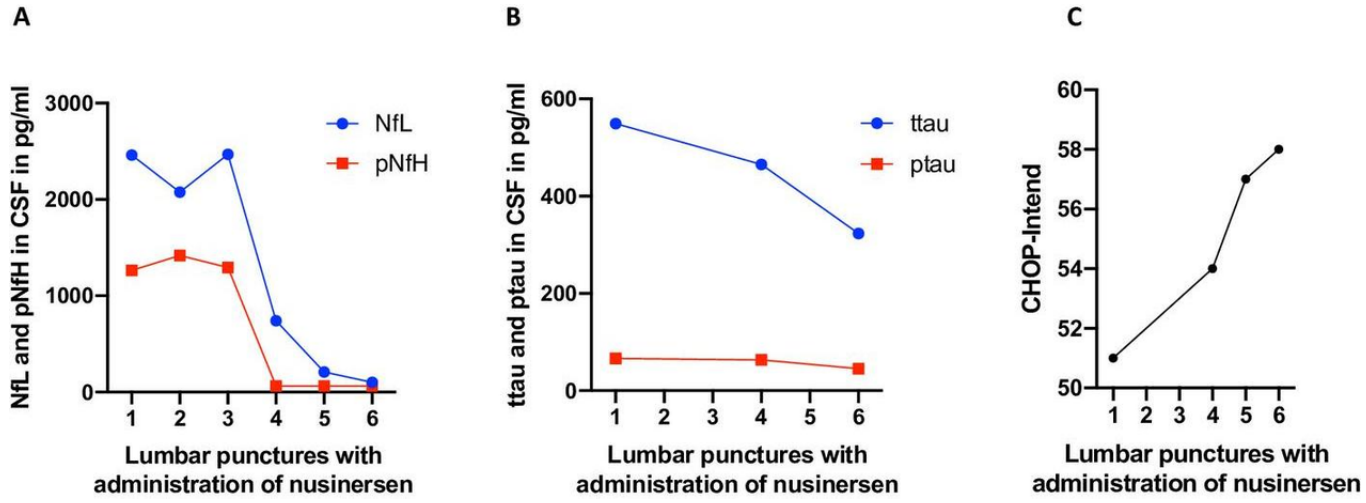

Figure 1 Course of neurofilaments (NfL and pNfH) (A) and tau (ttau and ptau) (B); clinical course (C) (measured by the CHOP-Intend; the highest score to reach at CHOP-Intend is 64 points, lower values represent a more severe stage of disease) in a spinal muscular atrophy (SMA) type 1 infant under treatment with nusinersen. CHOP-Intend, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CSF, cerebrospinal fluid; NfL, neurofilament light chain; pNfH, phosphorylated neurofilament heavy chain; ptau, phosphorylated tau; ttau, total tau.

In baseline CSF, drained before the first administration of nusinersen, NfL values of 2460 pg/mL and pNfH values of 1263 pg/mL were measured. In the following lumbar punctures, Nf levels showed similarly high levels (NfL 2077 pg/mL and pNfH 1419 pg/mL in second CSF; NfL 2469 pg/mL and pNfH 1293 pg/mL in third CSF). However, in CSF of the fourth lumbar puncture (after 2 months of therapy), pNfH showed a decrease below the lower limit of detection of <62.5 pg/mL and remained below the lower limit of detection in CSF of the fifth and sixth lumbar punctures. In addition, NfL values in CSF decreased from 741 pg/mL (fourth lumbar puncture) to 209 pg/mL (fifth lumbar puncture) and finally below the lower limit of detection of <100 pg/mL (sixth lumbar puncture).

Baseline CSF ttau levels were 549 pg/mL and ptau levels 66 pg/mL. The values decrease in CSF of the fourth lumbar puncture to 465 pg/mL (ttau) and to 63 pg/mL (ptau) and in CSF of sixth lumbar puncture to 323 pg/mL (ttau) and to 45 pg/mL (ptau). Changes in motor score (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, CHOP-Intend) and levels of NfL, pNfH, ttau and ptau are demonstrated in figure 1.

It is of note that valid age-dependent ranges of Nf and tau values in CSF in infants are not evident so far. The importance of establishing appropriate reference values in infants becomes apparent here, from a clinical and scientific point of view, as it is also conceivable that these values may be elevated in healthy infants during neuromuscular maturation.

However, our data provide first evidence for elevated Nf and tau values in CSF in infantile-onset SMA, that decrease under treatment with nusinersen. Considering the clinical improvement under treatment of this girl, which would have not been possible in the spontaneous course of SMA type 1, it can be speculated that these parameters, most notably Nf, may be used as an additional marker for therapy monitoring in infantile-onset SMA. Further studies with a larger patient population will be needed to clarify this hypothesis.

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