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The Diagnostic and Therapeutic Management of Spinal Muscular Atrophy Patients Requires Comprehensive Examinations and Close Monitoring

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LETTER TO THE EDITOR

We were interested to read the article by Kim, *et al.*, on a retrospective study of the diagnostic process in 38 patients with spinal muscular atrophy (SMA) type II (n=9) and type III (n=19), conducted between January 2000 and September 2023 *[Kim, S. H. et al., 2024]*. The median age at disease onset and diagnosis was 3 and 25 years, respectively *[Kim, S. H. et al., 2024]*. The median delay in diagnosis was 19.6 years, which was significantly longer for SMA III (21 years) than for SMA II (3 years) *[Kim, S. H. et al., 2024]*. The median number of visits before diagnosis was 2 in both groups *[Kim, S. H. et al., 2024]*. It was concluded that early diagnosis of SMA is crucial given the availability of effective genetic treatments *[Kim, S. H. et al., 2024]*. The study is impressive, but some points should be discussed.

The first point is that it is unclear which differential diagnoses have been considered and whether they have been thoroughly excluded. Differential diagnoses of SMA that need to be considered and explicitly excluded include familial and sporadic amyotrophic lateral sclerosis (fALS, sALS), bulbar spinal muscular atrophy (BSMA), oculo-pharyngeal muscular dystrophy (OPMD), Guillain-Barre syndrome (GBS), especially the pharyngo-cervicobrachial subtype, X-linked infantile SMA, SMARD1-related muscle weakness, GARS1-related infantile SMA, Prader-Willi syndrome, Zellweger spectrum disorder, congenital myasthenic syndrome, Pompe disease, botulism, Duchenne muscular dystrophy, hexosaminidase A deficiency, Fazio-Londe syndrome and riboflavin transporter deficiency *[Prior, T. W. et al., 2024]*.

Secondly, it is incomprehensible why in the cohort of SMA III patients the diagnosis was only made after a median time of 21 years. Since SMA is a progressive disease, patients, caregivers and treating physicians should be under pressure to make the correct diagnosis, not only to initiate optimal treatment, but also to provide optimal genetic counseling for these patients. Weren't patients under pressure to see a neurologist more often?

The third point is that it is not understandable why the mean number of visits before diagnosis was only 2 in both cohorts. Particularly in SMA III, one would expect affected patients to consult a neurologist more than twice with a median time between disease onset and genetic diagnosis of 21 years. Was this low number of visits due to the low number of neurologists available, was it due to a lack of patient interest or simply because the disease courses in the included patients were not progressive enough?

The fourth point is that it was not stated what type of ventilation was given to the five patients with SMA II and the four patients with SMA III. Did these patients receive oxygen only during the day or at night, continuous positive airway pressure (CPAP), non-invasive positive pressure ventilation (NIPPV), bilevel positive pressure ventilation or mechanical ventilation *[Groß, M. et al., 2019]*? Did the invasiveness of ventilation or the degree of respiratory insufficiency correlate with the number of SMN2 copies?

The fifth point is that it was not discussed that the diagnosis of SMA should also include tests of respiratory function, nerve conduction studies of the phrenic nerve and needle electromyography of the diaphragm and paraspinal muscles *[Zhuang, L. et al., 2002]*.

In summary, the index study has limitations that put the results and their interpretation into perspective. Addressing these limitations could strengthen the conclusions and support the results of the study. The diagnostic and therapeutic management of SMA patients requires comprehensive examinations and frequent close follow-up. If patients receive nusinersen,

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onasemnogene or rispdiplam, the frequency of follow-up examinations must be even higher.

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