

Case Report of Siblings With Infantile-Onset Niemann-Pick Type C (I-NPC) Initiating Adrabetadex at Different Ages and Intervals From Disease Onset

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Poster
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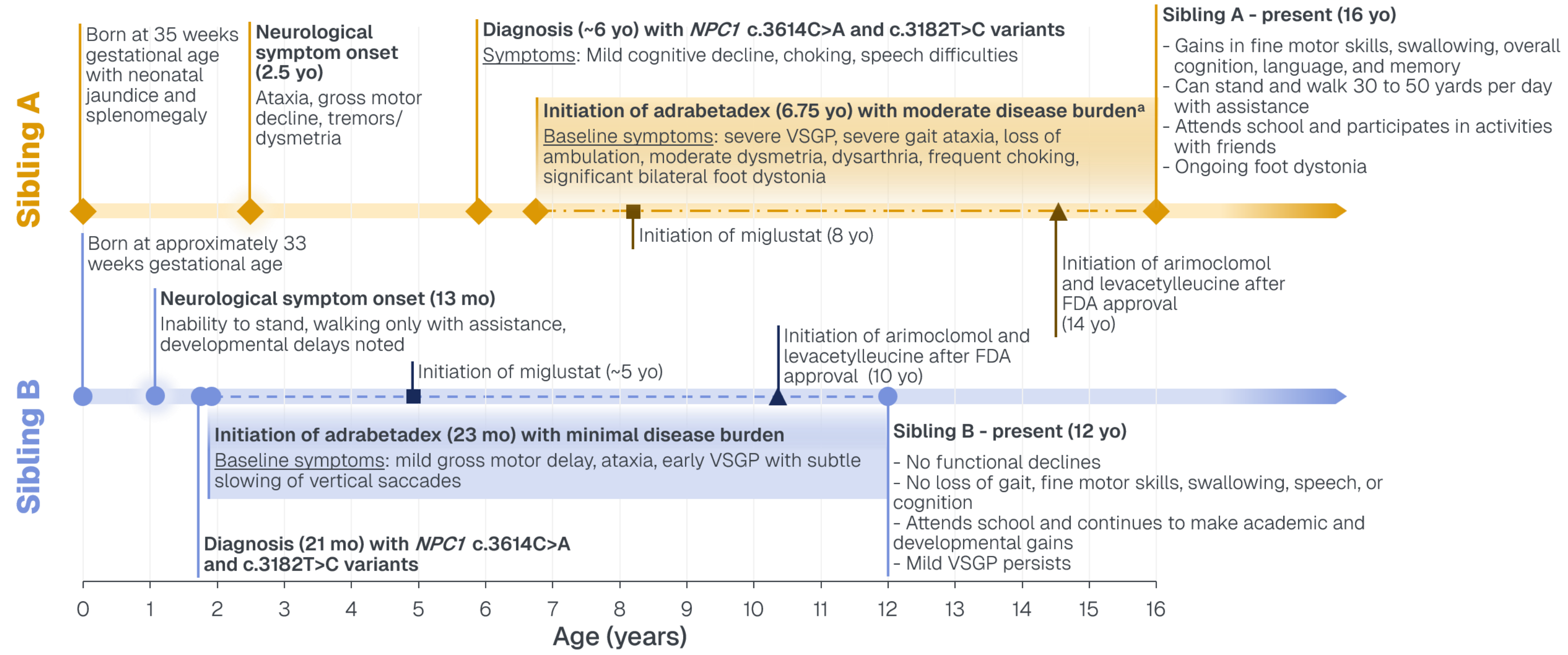
BACKGROUND

- Niemann-Pick disease type C (NPC) is a rare, progressive, neurodegenerative genetic disorder caused by impaired cholesterol trafficking, resulting in cholesterol accumulation and downstream cellular dysfunction.¹
- The rate of disease progression in NPC correlates with age of onset; infantile-onset NPC (I-NPC; neurological symptom onset <6 years of age) is associated with the most rapid neurodegeneration, accelerated clinical progression, and markedly increased risk of premature mortality.¹
- Because cholesterol accumulation occurs prior to progressive neuronal cell loss and neurodegeneration,^{2,3} early targeting of cholesterol trafficking may improve long-term clinical outcomes in I-NPC.
- Adrabetadex acts to restore intracellular cholesterol trafficking, the underlying pathological driver of NPC, and is administered intrathecally to achieve central nervous system exposure.
- Adrabetadex has been shown to significantly prolong survival and slow neurological disease progression in I-NPC.⁴
- This case report describes the impact of early diagnosis and initiation of adrabetadex in two female siblings with a confirmed diagnosis of I-NPC with *NPC1* c.3614C>A and c.3182T>C variants and provides insight into whether the timing of treatment initiation relative to disease onset influences outcomes in I-NPC.

CASE PRESENTATION

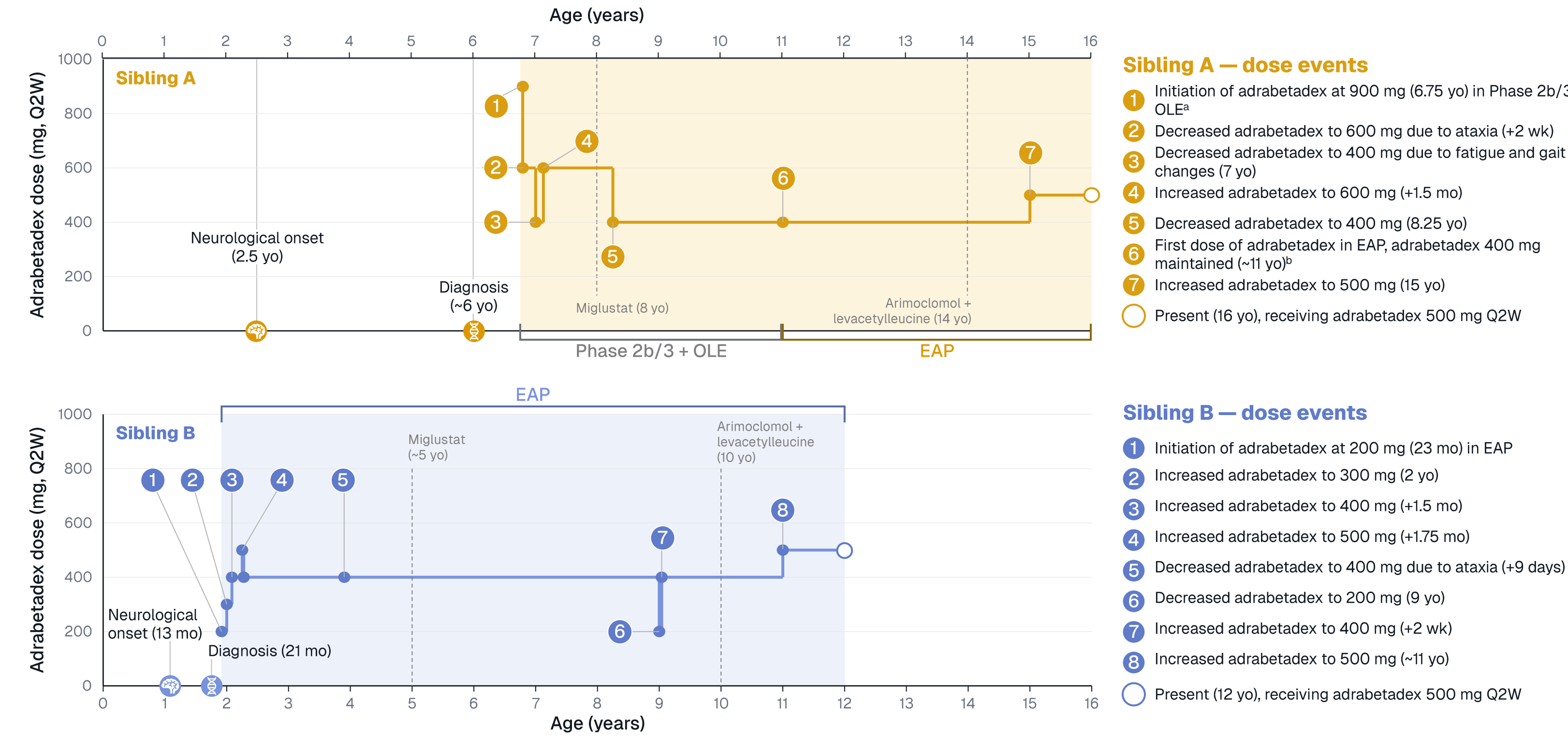
For all Figures: Stabilized or improved Stabilized with minimal symptoms

Figure 1. Clinical Courses



^aSibling A initiated adrabetadex in the Phase 2b/3 OLE. When initiated adrabetadex via EAP: ability to stand and ambulate with support, improved cognitive function compared to pre-treatment, progression of foot dystonia. Abbreviations: EAP=expanded Access Program; FDA=United States Food and Drug Administration; mo=months old; OLE=open-label extension; VSGP=vertical supranuclear gaze palsy; yo=years old.

Figure 2. Titration Schedule and Dosing Variation for Adrabetadex



^aSibling A initiated adrabetadex in the Phase 2b/3 OLE after being randomized to sham control in the Phase 2b/3 double-blind period and meeting rescue criteria. ^bWhen initiated in the EAP (11 yo), Sibling A's adrabetadex dose was maintained at 400 mg from her previous dose. Abbreviations: EAP=Expanded Access Program; mo=months; OLE=open-label extension; Q2W=every 2 weeks; wk=weeks; yo=years old.

CONCLUSIONS

- Earlier initiation of adrabetadex for Sibling B (approximately 10 months from neurological symptom onset) led to maintenance of minimal disease activity after 10 years compared to an estimated age of death of 5.6 years without treatment.⁶ This contrasts with her sister's disease course (who had moderate disease burden at treatment initiation), demonstrating the importance of restoring cholesterol trafficking before neuronal cell loss and neurodegeneration occur.
- Even with adrabetadex initiation 4.3 years after symptom onset at a moderate disease burden with rapid progression prior to treatment, Sibling A had stabilization or improvement of her symptoms over 10 years on treatment with adrabetadex. Given that the estimated age of death in late infantile-onset NPC without treatment is approximately 13.4 years,⁶ this represents a clinically meaningful result.
- Despite an age of onset consistent with I-NPC, both siblings had preservation of neurological function for more than 10 years from initiation of treatment with adrabetadex, highlighting the long-term potential of adrabetadex treatment.
- These findings support the potential for early initiation of intrathecal adrabetadex to slow neurological disease progression and modify the natural history of I-NPC, the most rapidly progressive form of NPC that is associated with severe neurological decline and early mortality.

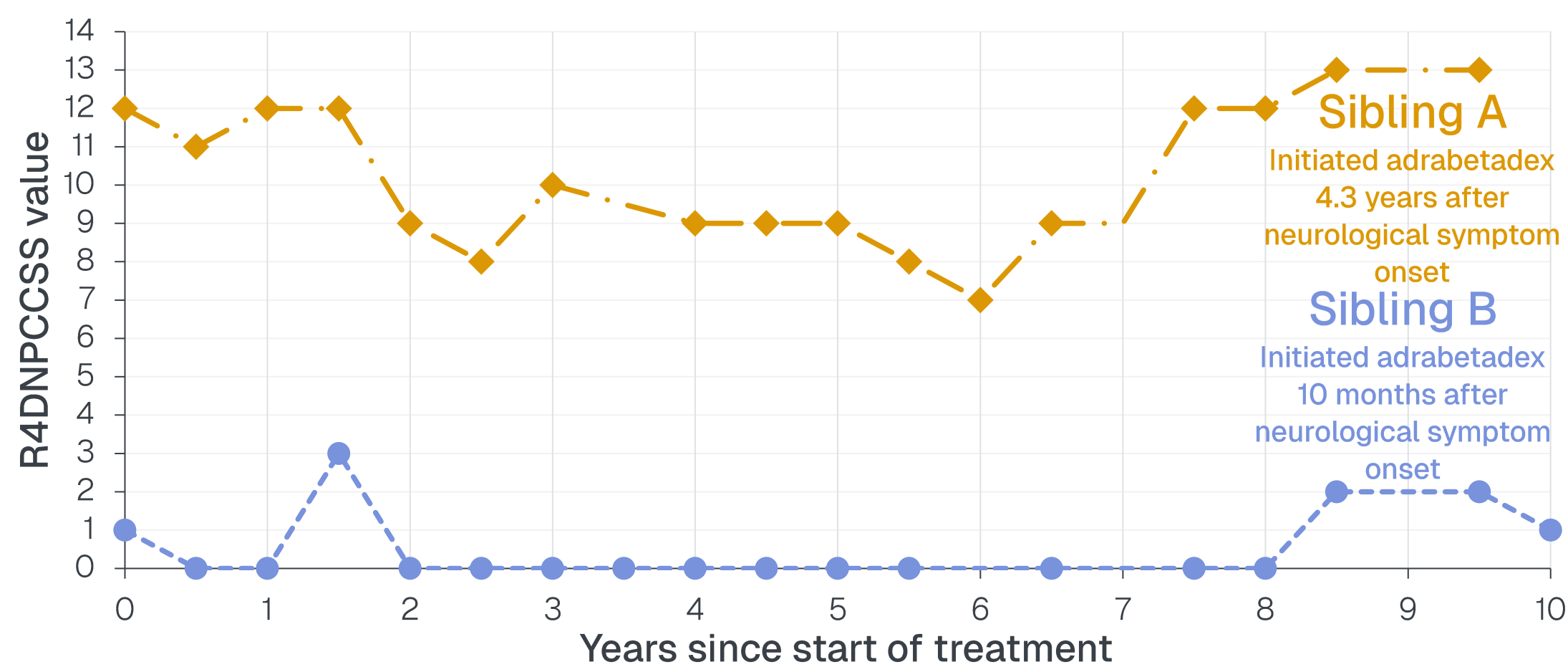
OBJECTIVE

- To describe the course of disease over ten years in two siblings with I-NPC, one with adrabetadex initiation 4.3 years after symptom onset (Sibling A) and one with initiation 10 months after symptom onset (Sibling B).

METHODS

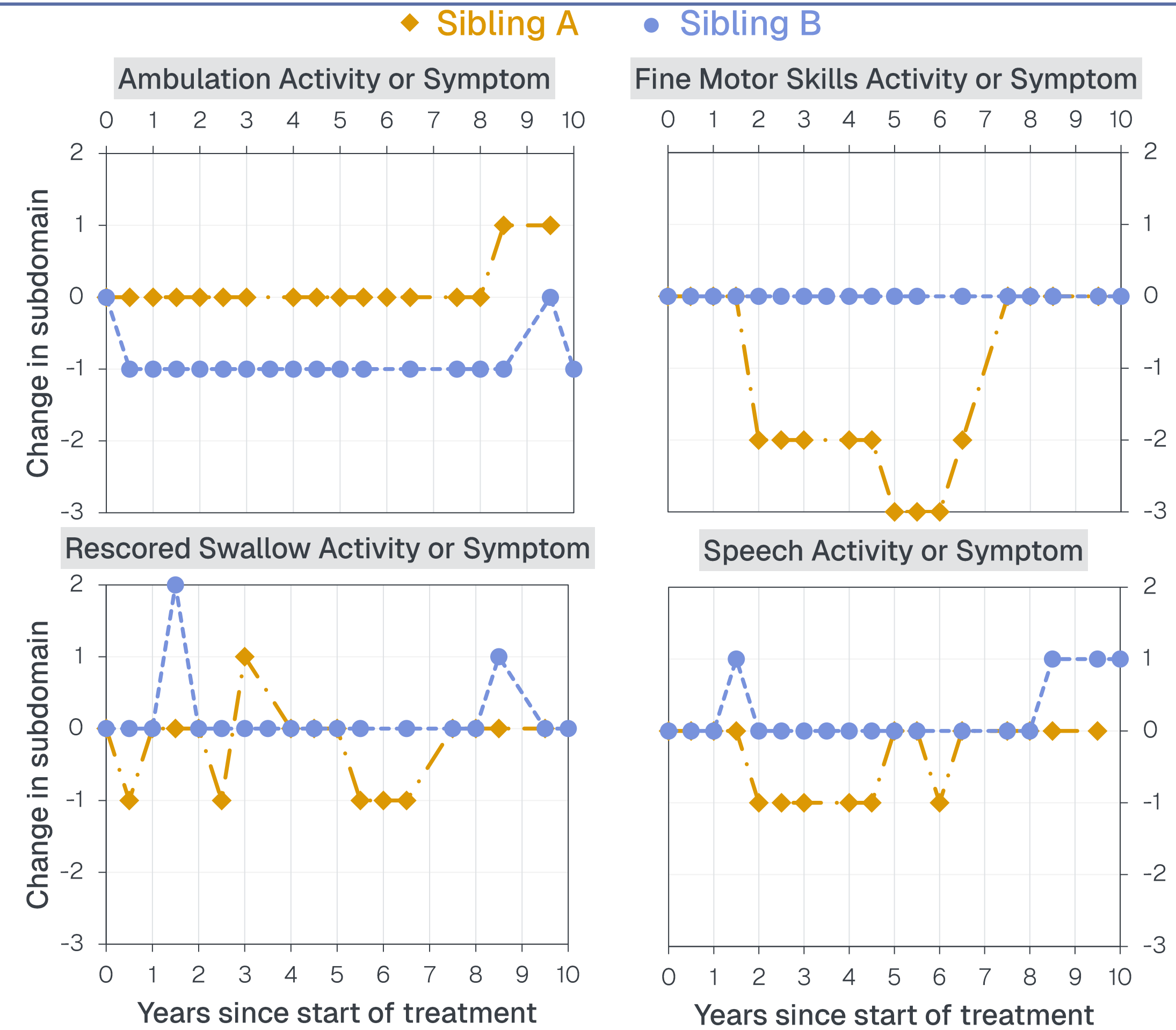
- Sibling A was enrolled in a Phase 2b/3 clinical trial and was randomized to the sham group. After approximately 7.5 months, she met rescue criteria and initiated intrathecal adrabetadex in the Phase 2b/3 open-label extension, approximately 4.3 years after the onset of neurological symptoms, at an initial dose of 900 mg every two weeks (Q2W). She subsequently enrolled in an Expanded Access Program (EAP) and continued to receive adrabetadex. Sibling A currently receives adrabetadex 500 mg Q2W in the EAP.
- Sibling B initiated intrathecal adrabetadex in the EAP approximately 10 months after neurological symptom onset, at an initial dose of 200 mg Q2W. Sibling B currently receives adrabetadex 500 mg Q2W in the EAP.
- Disease progression before and after adrabetadex initiation was monitored using the Rescored 4-domain Niemann-Pick disease type C Clinical Severity Scale (R4DNPCSS), a disease-specific clinical severity scale which assesses ambulation, fine motor skills, speech, and rescored swallowing.⁵
- Qualitative physician assessments were performed at each visit.

Figure 3. R4DNPCSS Composite Scores Over Time



Note: R4DNPCSS – Composite Outcome (Ambulation, Fine Motor, Rescored Swallowing, Speech). Higher scores indicate a greater degree of impairment. Abbreviations: R4DNPCSS=Rescored 4-domain Niemann-Pick disease type C Clinical Severity Scale.

Figure 4. Change in R4DNPCSS Subdomain Scores From Start of Adrabetadex



Note: R4DNPCSS – Subdomains (Ambulation, Fine Motor, Rescored Swallowing, Speech). Higher scores indicate a greater degree of impairment. Abbreviations: R4DNPCSS=Rescored 4-domain Niemann-Pick disease type C Clinical Severity Scale

References

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