Motor neuron involvement threatens survival in spinocerebellar ataxia type 1

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Motor neuron involvement threatens survival in spinocerebellar ataxia type 1

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Spinocerebellar ataxias (SCAs) are progressive and fatal neurodegenerative diseases. The most frequent forms are polyglutamine SCAs due to expansions in coding CAG repeats: *ATXN1*/SCA1, *ATXN2*/SCA2, *ATXN3*/SCA3, *CACNA1A*/SCA6, *ATXN7*/SCA7, *TBP*/SCA17 and *ATN*/DRPLA. These SCAs show faster disease progression than SCAs which are due to conventional mutations or intronic expansions [1]. Among polyQ SCAs, SCA1 has the shortest survival rate [2] with the strongest risk factors for death being the presence of dysphagia and higher relative scores on the Scale for the Assessment and Rating of Ataxia (SARA) [3]. The aim of this study was to explore how the neurodegenerative process may explain shorter survival in SCA1 patients. Neuropathological studies indicate that brainstem involvement is a major feature in SCA1 [4], including the structures responsible for the process of swallowing [5]. Motor neurons of the brainstem and cervical spinal cord degenerate in SCA1 knock-in (*Atxn1*$^{154Q/+}$) mice, in particular in the hypoglossal nucleus (nucleus of cranial nerve XII) [6]. Impairment of the XII cranial nerve is involved in dysphagia and dysarthria. The different phases (lingual, pharyngeal and oesophageal) of swallowing are altered in almost all SCA patients with consequent dysphagia. Dysphagia represents a risk factor for aspiration pneumonia, weight loss and malnutrition and is usually alleviated by a nasogastric tube, parenteral nutrition or percutaneous endoscopic gastrostomy.

In this study, the patients underwent multimodal investigations and post-mortem analysis to understand how the neurodegenerative process threatened life in SCA1 patients.

We included 10 SCA1 patients (from 10 distinct families) with respiratory distress, all seen in the national reference centre for rare diseases at Pitié-Salpêtrière University Hospital in Paris over an 11-year period. They underwent (i) laryngofibroscopy and electromyography of the larynx muscles to explore laryngeal function; (ii) overnight polysomnography with a measure of the apnoea–

hypopnoea index (number of apnoea and hypopnoea episodes per hour slept, with an index higher than 30 designating severe sleep apnoea); (iii) chin electromyography to measure the percentage of rapid eye movement (REM) sleep without atonia, whether phasic or tonic [7]; and (iv) diaphragm function assessment; the diagnosis of diaphragmatic dysfunction was based on previously defined criteria [8].

Each participant consented in accordance with French legislation, and approval was received from the local ethic committee (Necker Enfant-Malades on 19/12/1990 and 10/11/1992 and followed by the Ethics committee Ile de France II on 30/9/2004 and 18/2/2010 to AD). Details for neuropathological methods are provided in Supporting Information S1.

The mean age at onset was 32.1 ± 17 years (17–67), the mean disease duration at examination was 14.7 ± 6.1 years (8–25) and the SARA score was 26.8/40 ± 6.75 (19–34) (Table 1). All patients had severe swallowing difficulties, including one patient with a feeding tube. Patients did not report behavioural REM sleep disorders. The mean age at death was 51.0 years ± 23.2 (29–88, $n = 10$), after a mean disease duration of 18.9 years ± 8.0 (10–34, $n = 10$). The causes of death were aspiration pneumonia ($n = 5$), complications from gastroscopy ($n = 1$) and unknown ($n = 4$). CAG repeat size was inversely correlated with the age at death ($r = -0.87$, $p = <0.001$).

Laryngoscopy was performed after a mean disease duration of 15.7 ± 6.3 years and a mean SARA score of 26.3 ± 6.4 ($n = 7$) and showed a failure to abduct the vocal cords in all participants, with a resulting narrowing of the glottic airway ($n = 3$) and inspiratory stridor ($n = 2$). Electromyography confirmed laryngeal dystonia ($n = 3$), motor neuron denervation ($n = 3$) and laryngeal diplegia ($n = 1$). Dystonia resulted from increased activity of the thyroarytenoid and/or posterior cricoarytenoid muscles. Botulinum toxin injection into the involved muscles provided transitory improvement in dysphonia and dyspnoea in two patients. Posterior cordotomy was performed for one patient, and for two additional patients, autologous fat grafts in the vocal cords improved symptoms.

Overnight polysomnography was performed after a mean disease duration of 12.5 ± 4.8 years with a mean SARA score of 28.4 ± 5.5 and a body mass index of 23.8 ± 3.2 kg/m^2 ($n = 6$). Total sleep time, duration of wakefulness after sleep onset and sleep efficiency were within normal ranges, with the exception of one patient (326-79) who slept less than 70% of the night. The percentages of sleep stages N1, N2 and N3 were within normal ranges, but the percentage of REM sleep was lower (<15% of total sleep time) in four out of six patients (Table 1). The percentage of enhanced tonic plus phasic muscle chin activity during REM sleep was higher than normal (18% to 59%) in all six patients. The mean arousal index was 31 ± 16. The apnoea–hypopnoea index was below 5 in two patients, between 5 and 15 in three patients and between 15 and 30 in one patient (369-20). Diaphragmatic investigation ($n = 6$) revealed diaphragm dysfunction in three patients (326-79, 361-31 and 465-13), with lower oesophageal pressure (<11-cm H_2O) in response to bilateral phrenic stimulation. The first had phasic cervical respiratory accessory muscle activation. All had delayed central motor conduction (i.e., prolonged latency of diaphragmatic motor evoked potentials in response to transcranial magnetic stimulation of 24.7, 27.7 and 16 ms), suggesting impairment in the upper motor neuron pathway. There was no neuropathy on the electromyogram nor was there abnormal phrenic nerve conduction. In two cases, REM sleep percentages were lower than normal (4.8% and 4%). The minimal oxyhaemoglobin saturation during REM sleep was between 89% and 91% in these patients. Both died of acute respiratory failure.

We analysed the medulla oblongata in three SCA1 patients (detailed neuropathological examinations in Supporting Information S1) to investigate motor neuron density, especially in the hypoglossal nucleus. The ages at death were 29, 51 and 68 years after a disease duration of 9, 21 and 25 years and a pathological *ATXN1* CAG repeat size of 63, 49 and 48, respectively. We compared the findings with those obtained in three control cases (ages at death 54, 58 and 60 without neurological diseases).

Compared with controls, motor neuron degeneration was evident in SCA1 brainstems with smaller medulla oblongata surface area and motor neuron depletion, especially in the hypoglossal nucleus (Figures 1 and S1).

This study aimed to explore the life-threatening conditions present in SCA type 1. We enrolled only SCA1 patients with respiratory distress. Dysphagia was the most common alteration, found in all patients, followed by dyspnoea and dysphonia. Laryngeal dysfunction was present in all patients which included glottis leak, vocal cord paralysis, laryngeal hypotonia, vocal cord spasm in adduction, inspiratory stridor and vocal cord abduction weakness. We found that the most significantly life-threatening complication was laryngeal dysfunction, causing swallowing and respiratory dysfunction and death from aspiratory pneumonia. These findings should aid in clinical

Key points

- This study aimed to explore life-threatening conditions in spinocerebellar ataxia type 1.
- Laryngeal dysfunction was severe in all patients and was the most life-threatening condition, causing swallowing and respiratory dysfunction and death as a result of aspiratory pneumonia.
- Sleep disturbance may be caused by progressive loss of pontine REM-on neurons.
- Investigation of the diaphragm suggested impairment in the upper motor neuron pathway.
- Quantified neuronal loss was severe in the medullary tegmentum, with especially massive neuronal loss in the inferior olivary nucleus and the hypoglossal motor nucleus.
- Brainstem involvement with severe motor neuron depletion may explain life-threatening conditions in SCA1 patients.

TABLE 1 Clinical and multimodal explorations of spinocerebellar ataxia type 1 patients with respiratory distress.

ID	395-5	326-79*	721-10	302-15	347-11	369-20*	860-17*	361-31	399-818	465-13
ATXN1 CAG repeats (pathological/normal)	66/29	63/30	57/30	56/31	50/29	49/29	48/29	45/29	39/32	39/22
Disease duration (years)	8	8	8	10	25	19	19	13	20	17
SARA score (max value 40)	32	31	19	24	34	34	29.5	29.5	19	21
Pyramidal signs	+	+++	++	++	++	+++	++	++	++	++
Extrapyramidal signs	−	+++	++	+	−	+	++	−	−	−
Lingual fasciculation	++	++	++	++	++	−	++	++	−	−
Cognitive impairment	−	++	−	−	+	−	+	+	−	+
Dysphonia	+	−	−	−	+	−	+	−	+	−
Dysphagia	+++	++	++	++	++	++	++	+	++	++
Dyspnoea	+	+	+	+	++	+	++	++	++	++
Laryngofibroscopy	Laryngeal hypotonia and spasms	nd	Glottic leak	nd	Failure to abduct the vocal cords, IS	nd	VP, glottic leak	NGA, laryngeal diplegia	Failure to abduct the vocal cords, NGA, IS	NGA
Larynx EMG	nd	nd	LD	nd	MN	nd	MN	LD	MN	LD
Apnoea–hypopnoea index	1	8	nd	13	nd	29	nd	3	nd	12
Apnoea–hypopnoea index in REM sleep	9	13	nd	4	nd	5	nd	11	nd	32
Periodic leg movements during sleep (N/h)	32	19	nd	3	nd	39	nd	84	nd	33
Arousal index (N/h)	13	32	nd	34	nd	50	nd	13	nd	46
REM sleep (% of total sleep time)	13	4	nd	21	nd	13	nd	20	nd	4
REM sleep without atonia (% of REM sleep)	59	24	nd	26	nd	36	nd	37	nd	18
Cortico-diaphragmatic CT (from transcranial magnetic stimulation) (ms)	nd	24.7	nd	nd	nd	nd	nd	27.7	nd	16
Phrenic nerve CT (from cervical magnetic stimulation) (ms)	7.75	6.4	nd	6.25	nd	6.65	nd	6.3	nd	6

Abbreviations: CT, conduction time; DD, disease duration; EMG, electromyography; IS, inspiratory stridor; LD, laryngeal dystonia; MN, motor neuronal denervation; nd, not done; NGA, narrowing of the glottic airway; REM, rapid eye movement; VP, vocal cord paralysis. +, mild; ++, moderate; +++, severe.
*Patients with autopsy.

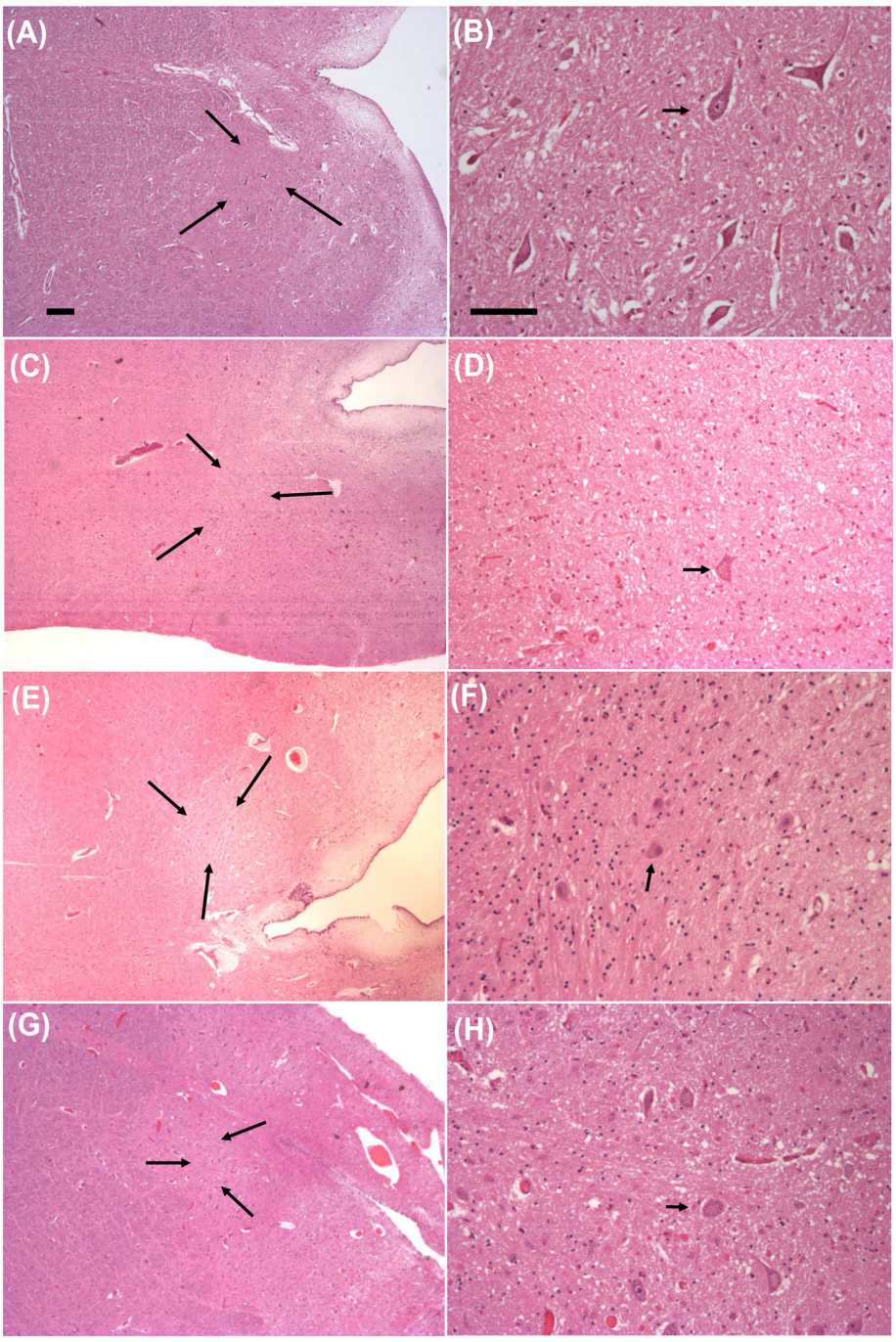

FIGURE 1 Comparison of the hypoglossal nucleus in SCA1 patients and control. Haematoxylin–eosin staining. (A, C, E, G) The ×2 objective, scale bar: 200 µm. (B, D, F, H) The ×10 objective; scale bar: 100 µm. (A, B) Control case, 60 years at death. (A) The black arrows delineate the limits of the hypoglossal nucleus. At higher per view (B), normal motor neurons. (C, D) Patient 369-20, 51 years at death, *ATXN1* pathological expansion of 49 CAG repeats (normal allele 29). In (C), the surface area of the hypoglossal nucleus (black arrows) appears smaller. In (D), neurons are smaller and chromatolytic (arrow). (E, F) Patient 326-79, 29 years at death. *ATXN1* pathological expansion of 63 CAG repeats (normal allele 30). In (E), the nucleus appears atrophic (black arrows) and pale. The number of neurons is reduced (F), one of which (arrow) is chromatolytic. (G, H) Patient 860-17, 68 years at death, *ATXN1* pathological expansion of 48 CAG repeats (normal allele 29). In (G), the hypoglossal nucleus is smaller and pale. Chromatolytic motor neurons are present (arrow).

management: Early detection of dysphagia, dysphonia and dyspnoea should be anticipated and thoroughly investigated. Taking precautions to avoid aspiration pneumonia and, consequently, recurrent hospital admissions could improve the quality of life of these patients. Detection of vocal cord abnormalities is essential in order to propose symptomatic treatments such as botulinum toxin, posterior cordotomy, autologous fat graft in the vocal cord and, eventually, tracheotomy. For respiratory and sleep alterations, nocturnal ventilator assistance should be considered, based on polysomnographic studies.

These alterations are similar to those seen in other polyglutamine SCAs and multiple system atrophy patients [9, 10]. Loss of bulbospinal motor neurons is thought to be responsible for the neurogenic atrophy of laryngeal muscles [9]. In particular, the hypoglossal nucleus extends the length of the medulla and innerves the intrinsic and extrinsic muscles of the tongue (except for the palatoglossus), which are essential for mastication, speech, swallowing and upper airway airflow during sleep. [11].

A notable exception to bulbar motor neuron loss is in SCA6 [4] which has a less severe phenotype. In SCAs, clinical features, found by the different investigations, are well correlated with the neuropathology: atrophy of the brainstem, neuronal loss in the cranial nerve nuclei, including the ambiguous and hypoglossal nuclei, pyramidal

tract reduction, loss of neurons in the substantia nigra, spinocerebellar tract thinning, moderate depletion of Purkinje cells, neuronal loss in the dentate nucleus and neuronal rarefaction in the anterior horn of spinal cord. Post-mortem examination of the three SCA1 patients in our study matches the characteristics found in previous neuropathological studies [12, 13].

Some specific sleep alterations, including the reduced percentage of REM sleep, increased arousal and REM sleep without atonia, may be caused by the progressive loss of pontine REM-on neurons (non-motor neurons) because the locus coeruleus appeared normal. In addition, deficiency in the genioglossus muscle (innervated by the hypoglossal nerve), a muscle that usually prevents decreases in airflow and pharyngeal collapse, may increase the risk of obstructive sleep apnoea syndrome; however, this occurrence was rare. This is the case in SCA1 because apnoea–hypopnoea events are associated with increased disease severity despite the absence of typical risk factors like advanced age or obesity [14]. The diaphragm, which is not inhibited during REM atonia, is the single inspiratory muscle active during REM sleep. This muscle was dysfunctional in three patients, resulting in decreased REM sleep percentages in two. This deficit was not related to the presence of neuropathy but probably to the degeneration of upper and lower motor neurons like in amyotrophic lateral sclerosis.

The small number of patients limits the generalisability of our conclusions. However, SCA patients are rare and attaining the inclusion criterion of respiratory distress was difficult, as at that stage of the disease, patients are severely functionally impaired and therefore difficult to include in research.

In conclusion, laryngeal dysfunction causing respiratory and swallowing failure was evident in our patients. Neuropathological findings explain these conditions showing significant brainstem involvement in SCA1 with severe motor neuron depletion.

AUTHOR CONTRIBUTIONS

Giulia Coarelli: Data curation; formal analysis; writing–original draft. **Maya Tchikviladzé:** Investigation; data curation; formal analysis; writing–review and editing. **Pauline Dodet:** Investigation; data curation, writing–review and editing. **Isabelle Arnulf:** Investigation; writing–review and editing. **Myriam Cohen:** Investigation; writing–review and editing. **Perrine Charles:** Investigation; writing–review and editing. **Frederic Tankeré:** Investigation; writing–review and editing. **Thomas Similowski:** Investigation; writing–review and editing. **Danielle Seilhean:** Writing–review and editing. **Alexis Brice:** Writing–review and editing. **Charles Duyckaerts:** Conceptualisation; methodology; writing–review and editing. **Alexandra Durr:** Conceptualisation; methodology; investigation; writing–review and editing.

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CONFLICT OF INTEREST STATEMENT

G.C., M.T., P.D., C.P. and F.T. report no competing interests. I.A. received consulting fees from IDORSIA Pharma. T.S. received consulting fees from ADEP assistance, Astra Zeneca, Chiesi France, KPL consulting, Lungpacer Inc., OSO-AI; honoraria from Chiesi France, Vitalaire France, TEVA France; patents WO2008006963A3, WO2012004534A1, WO2013164462A1; AUSTRAL Dx, HEPHAI. D.S. received grant IBISA 2021, patent USA17/606554. A.B. received France Parkinson FRC Grant, Grant ANR - EPIG - Agence nationale de recherche, Grant ANR - JPND - Agence nationale de recherche, Institut de France. A.D. received Grant NIH (U01 NS104326), Biogen/Ionis – CERMOI, Triplets Therapeutics, National Hospital Clinical Research Program - CREAM-HD, ROCHE 2019 – GENERATION-HD, WAVELife 2019 – PRECISION-HD, ANR E-Rare – PROSPAX; consulting fees from Wavelife therapeutics, Askbio, UCB, Roche; patent B 06291873.5; President of "Societé Francophone de Neurogénétique."

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author (alexandra.durr@icm-institute.org) upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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