

Autonomic nervous system dysfunction in motor neuron diseases

Alexandra Prufer de Queiroz Campos Araujo^{1*}, Igor Prufer de Queiroz Campos Araujo², Abelardo de Queiroz Campos Araujo³

¹Institute of Pediatrics, Federal University of Rio de Janeiro (UFRJ). Rua Bruno Lobo 50, Cidade Universitária, Rio de Janeiro, RJ 21941-912, Brazil

²School of Medicine, Federal University of Rio de Janeiro (UFRJ) Rua Bruno Lobo 50, Cidade Universitária, Rio de Janeiro, RJ 21044-020, Brazil

³The Institute of Neurology, Federal University of Rio de Janeiro (UFRJ). Av Venceslau Braz, 215, Botafogo, Rio de Janeiro, RJ 22290-160, Brazil

Article Info

Article Notes

Received: October 04, 2017

Accepted: January 30, 2018

*Correspondence:

Dr. Alexandra Prufer de Queiroz Campos Araujo, Institute of Pediatrics, Federal University of Rio de Janeiro (UFRJ), Rua Bruno Lobo 50, Cidade Universitária, Rio de Janeiro, RJ 21941-912, E-mail: alexprufer@ufrj.br

© 2018 Araujo APQC. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License.

Keywords

autonomic nervous system
spinal muscular atrophy
motor neuron disease
animal models

ABSTRACT

Background: Motor neuron disorders predominately result in progressive weakness. Nevertheless a wider expression of symptoms and signs point to a more multisystemic involvement. Autonomic nervous system findings have been reported in animal models, adult and child motor neuron diseases.

Objective: Review the literature on autonomic findings in motor neuron diseases.

Method: A PubMed literature search.

Results: In the present review, we will discuss the neuropathological and clinical features of dysautonomia reported in motor neuron disease in humans and animal models.

Conclusion: The literature points to considering careful autonomic evaluation and management in patients with motor neuron disorders.

Background

Autonomic nervous system (ANS) disorders are found either as a primary disease or in association with other nervous system disorders. Dysautonomia is a general term used to describe a failure of the ANS. Symptoms are wide-ranging and unspecific; therefore these conditions are often misdiagnosed. The pathological involvement can be either central, involving structures as the intermediolateral (IML) column, the dorsal nucleus of the vagus and other brainstem nuclei, or peripheral postganglionic path¹.

Until recently, acquired and hereditary motor neuron diseases have been considered disorders clinically and pathologically limited to the motor neurons. However, this well established knowledge has been challenged by new clinical and experimental data. Recent evidences have led to believe that these conditions may have a wider range of involvement, also affecting the ANS². Finally, although expression of ANS occurs in primary motor disorders and sympathicomimetics may show benefit in motor performance³, it was not until recently, that a anatomical intersection of those two neurological systems have been found⁴.

In this review, we will focus on findings of dysautonomia in motor neuron diseases in general and in SMA, both in humans and in animal models.

Methods

For this review, the literature search was based on PubMed using the Mesh terms “Motor Neuron Disease”, “Bulbo-Spinal Atrophy, X-Linked”, “Muscular Atrophy, Spinal”, “Spinal Muscular Atrophies of Childhood”, “Autonomic Nervous System”, “Autonomic Dysreflexia”, “Autonomic Nervous System Diseases”, “Adrenergic Fibers”, “Parasympathetic Nervous System”, “Sympathetic Nervous System”, “Cholinergic Fibers”. Articles that did not refer to the specific topics were not included. Four articles that were not retrieved by the search were included as they were cited in others and/or considered to have important and pertaining results. The review is divided into three topics: Dysautonomia in motor neuron diseases in animal models, in Motor Neuron Diseases in adults and in Spinal Muscular Atrophies of Childhood.

Results

Animal models

Using animal models is an excellent way to test and prove an etiopathogenic hypothesis. To this end, the involvement of the ANS in motor neuron diseases has been explored particularly in Spinal Muscular Atrophy (SMA) mouse models⁴⁻⁹.

Heier et al⁵ found evidence of both myocardial and ANS disturbances present in *SMNDelta7* SMA mouse model. Bradyarrhythmia was present in SMA mice relative to unaffected heterozygous littermates from a postnatal second day and PR interval was significantly elongated at every time point electrocardiograms were recorded. Furthermore, immunostaining for sympathetic innervation showed a reduced number of branches in both ventral and dorsal heart views. Thus a decrease in sympathetic tone could be responsible for an autonomic imbalance.

Accordingly, slow heart frequency was also described by others, studying the same animal model⁶. Furthermore, delivery of a survival motor neuron-1 transgene using a self-complementary adeno-associated virus serotype 9 abolished this symptom. Thus authors conclude that this feature is most likely attributable to aberrant autonomic signaling.

In contrast, Biondi et al⁷, studying wild-type and type 2 SMA-like mice (*SmnDelta7/_7*; *SMN2+/-*) although also showing that cardiac and respiratory function are impaired in SMA-like mice, suggest that there is no defect in sympathetic activity and that differences in heart rate are more likely due to cardiac conduction defects. They used pharmacological inhibition of both sympathetic (atenolol) and parasympathetic (atropine) branches and an exercise protocol.

The impact of Survival Motor Neuron Protein (SMN-

PTN) deficiency was examined on gastroenteric function in the *SMNDelta7* SMA mouse model. This animal model produces drier and fewer fecal pellets when compared to the control mice. Also *SMNDelta7* mice had delayed gastric emptying and slow liquid transit in the small intestine. Central nervous system gene therapy did not rescue the gastroenteric dysfunction, suggesting a direct effect of SMN-PTN deficiency in the enteric nervous system⁸.

Additionally, distal necrosis, a feature of SMA mice models, is thought to be a result of ANS dysfunction producing impaired vascularization⁹.

Finally, in mice, skeletal muscle receives innervation from sympathetic neurons at the neuromuscular junction, where beta2-adrenoreceptors are depicted on confocal microscopy and a trophic role for this interaction is postulated⁴.

In summary, a number of animal models provided strong evidences of the involvement of the ANS in SMA.

Dysautonomia in Motor Neuron Diseases of adults

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder, rarely associated with specific genetic mutations, that involves motor neurons in the cerebral cortex, brain stem and spinal cord. Degeneration of both lower motor neurons and upper motor neurons are crucial neuropathological features of ALS⁸. ALS has traditionally been considered to be a pure motor disease, in which sensory function and coordination remain intact¹⁰, and the existence of additional neurological manifestations or other organ involvements suggest an alternative diagnosis. However, it is increasingly recognized that non-motor manifestations may occur¹¹.

Symptoms of dysautonomia are not prominent in ALS but were recently reported in several studies. Evidence for involvement of the ANS has also accumulated¹².

Autonomic symptoms such as orthostatic hypotension or postural dizziness are rare in patients with ALS¹³. However, advanced cases exhibit blood pressure fluctuations, including paroxysmal hypertensive episodes accompanied by tachycardia, as well as sudden falls in blood pressure. These frequently occur during sleep^{13,14}. In this way, a consistent body of evidences has suggested that enhanced sympathetic drive of presumably central origin, and possibly reduced parasympathetic drive, characterize the autonomic cardiovascular state in ALS¹².

ALS patients often report increased or reduced sweating in their palms, reduced skin temperature, or skin discoloration and studies of sudomotor function have provided evidence of sympathetic postganglionic cholinergic denervation in this disease¹⁵⁻¹⁷.

Within the spectrum of neuropathology, the ANS

appears to be the least frequently and systematically studied, although modern morphological techniques may be applied to evaluate its changes. This is partly due to limited access to the ANS via biopsy and partly because of lack of extensive sampling at autopsy. Nevertheless, in analogy to the loss of motorneurons, morphometric studies have detected neuronal loss in the thoracic^{18,19} and sacral²⁰ IML nucleus of the spinal cord, which contain sympathetic and parasympathetic preganglionic neurons, respectively. On the other hand, atrophic neurons with intracytoplasmic inclusions such as Bunina bodies have been documented in Onuf's nucleus²¹. Using a monoclonal antibody that specifically binds phosphorylated high molecular weight neurofilament proteins, Itoh et al.²² found that the IML column neurons in ALS also exhibited increased immunoreactivity compared with control individuals. Sympathetic ganglion neurons exhibited similarly high immunoreactivity for phosphorylated high molecular weight neurofilament in all studied individuals. A unique patient with ALS and a SOD1 (V118L) mutation which has developed autonomic failure exhibited marked neuronal loss in autonomic nuclei in the medulla and the IML column²³. These findings suggest that neurons that are involved in autonomic functions are vulnerable to the disease process in both sporadic and genetic ALS.

There is evidence for subclinical involvement of both sympathetic and parasympathetic nervous systems in ALS. Decreased heart rate variability and baroreceptor sensitivity, as well as abnormalities in gastrointestinal tract and salivary and lacrimal gland function indicate parasympathetic deterioration. Increased noradrenaline levels and muscle sympathetic nerve activity support the assumption of sympathetic hyperactivity, but evidence for postganglionic sympathetic deterioration, as indicated by cardiac sympathetic denervation, abnormal sympathetic skin response and sudomotor dysfunction, reflect sympathetic deterioration. Most reported abnormalities have not been found to correlate with disability score, disease duration, mode of involvement, or severity. Rather limited numbers of patients were included in the studies reviewed above. Furthermore, autonomic function may be additionally compromised by inactivity, difficulties in food intake and breathing problems, which are often encountered in ALS patients, particularly in advanced stages.

In summary, clinically significant autonomic disturbances are infrequent in early ALS. Effective compensatory mechanisms in the ANS and diminished daily activity may explain why the subtle autonomic dysfunction does not manifest clinically.

Another disease of the motor system, the spinal and bulbar muscular atrophy (SBMA), or Kennedy's disease, is a slowly progressive X-linked neuromuscular disease

caused by a trinucleotide repeat expansion in the androgen receptor gene. Affected males typically develop weakness in their mid-forties, as well as evidence of androgen insensitivity with reduced fertility and gynecomastia. SBMA causes a progressive degeneration of the lower motor neurons and muscle. ANS involvement has not been considered part of SBMA. Recently, however, Rocchi et al.²⁴ assessed the autonomic cardiovascular function in 5 SBMA patients. Autonomic function tests were abnormal in 4/5 patients, and plasma noradrenaline concentration was significantly reduced in patients when compared to controls. The impairment of cardiovascular responses in addition to reduced plasma noradrenaline concentration observed in those patients suggests subclinical involvement of the ANS in Kennedy disease²⁴ but this study awaits further confirmation.

Spinal muscular atrophies of childhood

SMA is widely known as a motor neuron disorder and is the most common example of motor neuron disease in children and adolescents. SMA is an autosomal recessive disorder, which is the leading genetic cause of infantile death. It occurs as a result of homozygous mutation of the survival motor neuron gene (*SMN1*), marked by progressive degeneration of motor neurons in the spinal cord resulting in weakness and muscular atrophy. The severity of the disease is related to the residual amount of SMN-PTN produced by the homologous gene (*SMN2*). SMN-PTN is ubiquitous and probably required for most tissues in normal development²⁵.

Signs and symptoms potentially related to dysautonomia have been reported in SMA, such as tachycardia/bradycardia, fluctuation of blood pressure, hyperhidrosis, abnormal finger cold-induced vasodilation, gastroesophageal reflux, constipation and delayed gastric emptying, abnormalities in vascular perfusion²⁶⁻³⁰.

Probably the first report on ANS features in SMA was of two young adults with SMA type III with atrial arrhythmias and atrioventricular conduction disturbances³¹. Atrioventricular conduction block and tachycardia were both also reported more recently by other authors³².

It is in the longer survival SMA type I patients that the involvement of the ANS is more evident. Hachiya et al.²⁶ report the findings of autonomic function test on 3 of those children. Measurement of blood pressure, heart rate shows remarkable fluctuation, as well as high plasma catecholamine during tachycardia and tilting, abnormal finger cold-induced vasodilatation. Taken together, these data suggest sympathetic hyperactivity and/or sympathetic-vagal imbalance.

Further, in a large retrospective study of SMA type I ventilated patients, a quarter of them presented severe

symptomatic bradycardia³⁰. Finally, digital necrosis, reported in SMA type I patients, is, according to the authors, dependent of impaired regulation of vascular tone, a function of the ANS^{28,29}.

Despite this evidence, others, exploring cardiac evaluation with electrocardiogram and echocardiography in a case series of 37 SMA type II/III aged 6 to 65 years, found no dysfunction³³.

Spinal muscular atrophy with respiratory distress (SMARD) is a rare motor neuron disease of infants that can also result in dysautonomia. Autonomic crisis has been reported³⁴, in a child with SMARD and previous heart rate variability and absent typical circadian rhythm.

Neuropathological data also suggest the involvement of ANS in SMA. A recent neuropathological postmortem study of SMA type 1 children revealed the wider spread presence of neuronal degeneration³⁵. The chromatolysis, degeneration and neuronophagia in the ventral thalamic nuclei previously shown^{36,37}, was confirmed, as well as lesions in the posteroventral thalamic nuclei, Clarke's column and spinal ganglion³⁸. Neurons in the sacral Onufrowicz's nucleus exhibit central chromatolysis^{39,40}. Additionally, neural tissue in the myenteric plexus of the small intestine and colon are significantly lower in SMA type 1 than in controls⁴¹.

Sympathomimetics have been used in some motor disorders with functional benefit, particularly on fatigue³. The recent findings of the presence of beta2-adrenoreceptors at the neuromuscular junction, help to understand the therapeutic effect of those drugs⁴.

In summary, the set of data presented so far suggest that SMA, previously conceived as having very specific topographical impact, may actually embrace a broader involvement.

Conclusions

Clinical reports suggest that other tissues contribute to the overall phenotype of motor neuron diseases, especially in the most severe or prolonged forms of these diseases. SMA as well as other motor neuron diseases must be regarded as associated with autonomic dysfunction in addition to motor neuron involvement. The most severe presentation of spinal muscular atrophy, if allowed to live long enough, shows the greatest widespread involvement.

The ANS is a potential vulnerable locus for different disease processes, which affect neurons. The symptoms related to ANS involvement are unspecific and multisystemic. The great challenge is to recognize the possibility of the ANS involvement, either because symptoms may impact quality of life and daily activities or because they might configure a higher risk of morbidity and mortality for the individual. Therefore, to include the questions on the

autonomic symptoms as well as specific assessment of its function, would help to define strategies to treat or prevent the consequences of ANS involvement. Careful autonomic evaluation and management are warranted in patients with motor neuron disorders.

Declarations

All authors participated in producing this work, from the literature review to article writing. Authors declare that they have no conflict of interest. No funding was received for this work. Since this work is a review, no original data is available.

References

- Bannister R. Degeneration of the autonomic nervous system. *Lancet*. 1971; 2(7717): 175-179.
- Shababi M, Lorson CL, Rudnik-Schöneborn SS. Spinal muscular atrophy: a motor neuron disorder or a multi-organ disease. *J Anat*. 2014; 224(1): 15-28.
- Pane M, Staccioli S, Messina S, et al. Daily salbutamol in young patients with SMA type II. *Neuromuscul Disord*. 2008; 18(7): 536-540.
- Khan MM, Lustrino D, Silveira WA, et al. Sympathetic innervation controls homeostasis of neuromuscular junctions in health and disease. *Proc Natl Acad Sci*. 2016; 113(3): 746-750
- Heier CR, Satta R, Lutz C, et al. Arrhythmia and cardiac defects are a feature of spinal muscular atrophy model mice. *Hum Mol Genet*. 2010; 19(20): 3906-3918.
- Bevan AK, Hutchinson KR, Foust KD, et al. Early heart failure in the SMNDelta7 model of spinal muscular atrophy and correction by post natal scAAV9-SMN delivery. *Hum Mol Genet*. 2010; 19: 3895-3905.
- Biondi O, Lopes P, Desseille C, et al. Physical exercise reduces cardiac defects in type 2 spinal muscular atrophy-like mice. *J Physiol*. 2012; 590(22): 5907-5925.
- Gombash SE, Cowley CJ, Fitzgerald JA, et al. SMN deficiency disrupts gastrointestinal and enteric nervous system function in mice. *Hum Mol Genet*. 2015; 24(13): 3847-3860.
- Somers E, Stencil Z, Wishart TM, et al. Density, calibre and ramification of muscle capillaries are altered in a mouse model of severe spinal muscular atrophy. *Neuromuscul Disord*. 2012; 22: 435-442.
- Brooks BR, Miller RG, Swash Met al. World Federation of Neurology Research Group on Motor Neuron Diseases. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Other Motor Neuron Disord*. 2000; 1: 293-299.
- Ince P. Neuropathology. In: Brown R, Meininger V, Swash M, editors. *Amyotrophic Lateral Sclerosis*. London: Martin Dunitz Ltd; 2000. p. 83-112.
- Baltadzhieva R, Gurevich T, Korczyn AD. Autonomic impairment in amyotrophic lateral sclerosis. *Curr Opin Neurol*. 2005; 18(5): 487-493.
- Shimizu T, Hayashi H, Kato S, et al. Circulatory collapse and sudden death in respirator-dependent amyotrophic lateral sclerosis. *J Neurol Sci*. 1994; 124: 45-55.
- Shimizu T, Kato S, Hayashi M, et al. Amyotrophic lateral sclerosis with hypertensive attacks: blood pressure changes in response to drug administration. *Clin Auton Res*. 1996; 6: 241-244.
- Beck M, Giess R, Magnus T, et al. Progressive sudomotor dysfunction in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry*. 2002; 73: 68- 70.

16. Kihara M, Takahashi A, Sugenoja J, et al. Sudomotor dysfunction in amyotrophic lateral sclerosis. *Funct Neurol*. 1994; 9: 193–197.
17. Santos-Bento M, de Carvalho M, Evangelista T, et al. Sympathetic sudomotor function and amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Other Motor Neuron Disord*. 2001; 2: 105–108.
18. Takahashi H, Oyanagi K, Ikuta F. The intermediolateral column cells in motor neuron disease and the Shy-Drager syndrome. *J Neurol*. 1993; 86: 190–192.
19. Kennedy PG, Duchon LW. A quantitative study of intermediolateral column cells in motor neuron disease and the Shy-Drager syndrome. *J Neurol Neurosurg Psychiatry*. 1985; 48: 1103–1106.
20. Konno H, Yamamoto T, Iwasaki Y, et al. Shy-Drager syndrome and amyotrophic lateral sclerosis. Cytoarchitectonic and morphometric studies of sacral autonomic neurons. *J Neurol Sci*. 1986; 73: 193–204.
21. Kihira T, Yoshida S, Yoshimasu F, et al. Involvement of Onuf's nucleus in amyotrophic lateral sclerosis. *J Neurol Sci*. 1997; 147: 81–88.
22. Itoh T, Sobue G, Ken E, et al. Phosphorylated high molecular weight neurofilament protein in the peripheral motor, sensory and sympathetic neuronal perikarya: system-dependent normal variations and changes in amyotrophic lateral sclerosis and multiple system atrophy. *Acta Neuropathol (Berl)*. 1992; 83: 240–245.
23. Shimizu T, Kawata A, Kato S, et al. Autonomic failure in ALS with a novel SOD1 gene mutation. *Neurology*. 2000; 54:1534–1537.
24. Rocchi C, Greco V, Urbani A, et al. Subclinical autonomic dysfunction in spinobulbar muscular atrophy (Kennedy disease). *Muscle Nerve*. 2011; 44: 737-740.
25. Wang CH, Finkel RS, Bertini ES, et al. Consensus statement for standard of care in spinal muscular atrophy. *J Child Neurol*. 2007; 22: 1027–1049.
26. Hachiya Y, Arai H, Hayashi M, et al. Ito Y, Uchiyama A, Kurata K. Autonomic dysfunction in cases of spinal muscular atrophy type 1 with long survival. *Brain Dev*. 2005; 27(8): 574-578.
27. Arai H, Tanabe Y, Hachiya Y, et al. Finger cold-induced vasodilatation, sympathetic skin response, and R-R interval variation in patients with progressive spinal muscular atrophy. *J Child Neurol*. 2005; 20: 871–875.
28. Araujo A P de Q C, Araujo M, Swoboda KJ. Vascular perfusion abnormalities in infants with spinal muscular atrophy. *J Pediatr*. 2009; 155: 292–294.
29. RudnikSchoneborn S, Vogelgesang S, Armbrust S, et al. Digital necroses and vascular thrombosis in severe spinal muscular atrophy. *Muscle Nerve*. 2010; 42: 144–147.
30. Bach JR. Medical considerations of long-term survival of Werdnig-Hoffmann disease. *Am J Phys Med Rehabil*. 2007; 86: 349–355.
31. Tanaka H, Uemura N, Toyama Y, et al. Cardiac involvement in the Kugelbert – Welander syndrome. *Am J Cardiol*. 1976; 38: 528–532.
32. Roos M, Sarkozy A, Chierchia GB, et al. Malignant ventricular arrhythmia in a case of adult onset of spinal muscular atrophy (Kugelberg-Welander disease). *J Cardiovasc Electrophysiol*. 2009; 20(3): 342-344.
33. Palladino A, Passamano L, Taglia A, et al. Cardiac involvement in patients with spinal muscular atrophies. *Acta Myol*. 2011; 30: 175–178.
34. Nomura T, Takenouchi T, Fukushima H, et al. Catastrophic autonomic crisis with cardiovascular collapse in spinal muscular atrophy with respiratory distress type 1. *J Child Neurol*. 2013; 28(7): 949-951.
35. Harding BN, Kariya S, Monani UR, et al. Spectrum of neuropathophysiology in spinal muscular atrophy type I. *J Neuropathol Exp Neurol*. 2015; 74(1): 15-24.
36. Towfighi J, Young RS, Ward RM. Is Werdnig-Hoffmann disease a pure lower motor neuron disorder. *Acta Neuropathologica*. 1985; 65: 270-280.
37. Murayama S, Bouldin TW, Suzuki K. Immunocytochemical and ultra- structural studies of Werdnig-Hoffmann disease. *Acta Neuropathologica*. 1991; 81: 408-417.
38. Rudnik-Schöneborn S, Goebel HH, Schlote W, et al. Classical infantile spinal muscular atrophy with SMN deficiency causes sensory neuronopathy. *Neurology*. 2003; 60: 983–987.
39. Chou SM, Kuzuhara S, Nonaka I. Involvement of the Onuf nucleus in Werdnig-Hoffmann disease. *Neurology*. 1982; 32: 880–884.
40. Sung JH, Matri AR. Spinal autonomic neurons in Werdnig-Hoffmann disease, mannosidosis, and Hurler's syndrome: distribution of autonomic neurons in the sacral spinal cord. *J Neuropathol Exp Neurol*. 1980; 39: 441–451.
41. Galvis DA, Ang SM, Wells TR, et al. Microdissection study of the myenteric plexus in acardia, ataxia- telangiectasia, cystic fibrosis, extrahepatic biliary atresia, pediatric AIDS and Werdnig-Hoffmann disease. *Pediatr Pathol*. 1992; 12: 385–395.