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Review

Multifaceted superoxide dismutase 1 expression in amyotrophic lateral sclerosis patients: a rare occurrence?

Ilaria Martinelli[1, 2], Jessica Mandrioli[1, 3, *], Andrea Ghezzi[3], Elisabetta Zucchi[1], Giulia Gianferrari[3], Cecilia Simonini[1], Francesco Cavallieri[4], Franco Valzania[4]

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From the Contents

Abstract

Amyotrophic lateral sclerosis (ALS) is a neuromuscular condition resulting from the progressive degeneration of motor neurons in the cortex, brainstem, and spinal cord. While the typical clinical phenotype of ALS involves both upper and lower motor neurons, human and animal studies over the years have highlighted the potential spread to other motor and non-motor regions, expanding the phenotype of ALS. Although superoxide dismutase 1 (*SOD1*) mutations represent a minority of ALS cases, the *SOD1* gene remains a milestone in ALS research as it represents the first genetic target for personalized therapies. Despite numerous single case reports or case series exhibiting extramotor symptoms in patients with ALS mutations in *SOD1* (*SOD1*-ALS), no studies have comprehensively explored the full spectrum of extramotor neurological manifestations in this subpopulation. In this narrative review, we analyze and discuss the available literature on extrapyramidal and non-motor features during *SOD1*-ALS. The multifaceted expression of *SOD1* could deepen our understanding of the pathogenic mechanisms, pointing towards a multidisciplinary approach for affected patients in light of new therapeutic strategies for *SOD1*-ALS.

Key Words: amyotrophic lateral sclerosis (ALS); autonomic; extramotor; genotype-phenotype; multisystem involvement; Parkinson's disease; sensory; SOD1; superoxide dismutase 1; urinary; vocal cord palsy

Introduction

Since its first description by Charcot in 1869, amyotrophic lateral sclerosis (ALS) has been considered a neurodegenerative disorder with isolated motor neuron involvement. In recent decades, it has been revealed that the core motor impairment in ALS may be accompanied by many non-motor symptoms (Goutman et al., 2022). In literature, reports have been found on multisystem presentation at onset, which poses a diagnostic challenge compared to the typical ALS and is associated with more severe disease (McCluskey et al., 2014). More frequently, extramotor signs may emerge from the longitudinal clinical observation of patients with unusually long survival in the context of sustained ventilatory and nutritional care, including abnormalities in eye movement, autonomic dysfunction, and sensory involvement (Swinnen and Robberecht, 2014). Interestingly, various mutations in ALS-related genes can be associated with specific motor and extra-motor phenotypes. For instance, *C9ORF72* expansions can lead to cognitive involvement, extrapyramidal signs, and seizures (Swinnen and Robberecht, 2014), suggesting that ALS might represent a multisystemic disease with a unique pathobiological basis (Mahoney et al., 2021). Even though literature encompasses numerous reports of individual cohorts exhibiting extramotor symptoms in ALS patients with mutations in the superoxide dismutase 1 gene (*SOD1*-ALS), no studies have comprehensively explored the full spectrum of extra-motor neurological manifestation in this subpopulation. In this narrative review, we aim to describe non-motor neuron abnormalities underlying *SOD1*-ALS, focusing on the identification, assessment, and monitoring of extramotor symptoms (**Figure 1**). We propose that recognizing these atypical features could enhance the management of knowledge-based care for ALS patients, shedding new light on the disease's pathogenesis and therapeutic targets.

Search Strategy

We conducted a bibliographical search on PubMed prior to January 1, 2023 using the core search terms "amyotrophic lateral sclerosis" or "ALS" and "superoxide dismutase 1" or "SOD1" combined with each of the following keywords separately: "histopathology," "autopsy," "multisystem," "extramotor," "urinary," "bladder," "autonomic,"

[1]Department of Neurosciences, Azienda Ospedaliero Universitaria di Modena, Modena, Italy; [2]Clinical and Experimental Medicine Ph.D. Program, University of Modena and Reggio Emilia, Modena, Italy; [3]Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy; [4]Neurology Unit, Neuromotor & Rehabilitation Department, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy

***Correspondence to:** Jessica Mandrioli, MD, jessica.mandrioli@unimore.it.
https://orcid.org/0000-0002-9244-9782 (Jessica Mandrioli)

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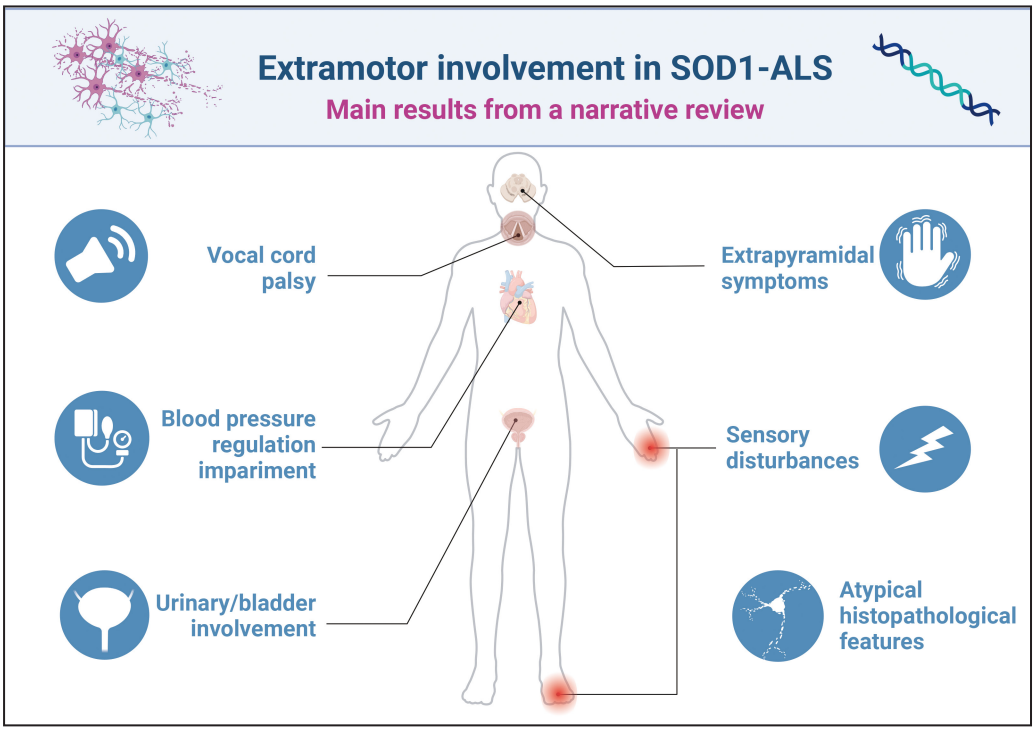

Figure 1 | Extramotor involvement in *SOD1*-ALS. Data are collected from a narrative review. Created with BioRender.com. ALS: Amyotrophic lateral sclerosis; SOD1: superoxide dismutase 1.

"dysautonomia," "sensory," "vocal cord palsy," "FOSMN," "Parkinson," "parkinsonism," "chorea," "dystonia," "tremor," "extrapyramidal," "tic," "ataxia," "cerebellar," "progressive supranuclear palsy," or "PSP," "multisystem atrophy" or "MSA," "corticobasal degeneration" or "CBD," "basal ganglia." The first screening of results was performed by titles and abstracts. Reviews, retrospective studies, single case reports, and case series were included. The search was then restricted to studies with full text available in the English language. Two independent researchers (IM and AG) performed the selection and review of the articles, extracted the information from each selected article, and summarized it into the present tables. Reference lists of selected papers were also searched for further leads.

Pathomechanism of Amyotrophic Lateral Sclerosis Associated with Superoxide Dismutase 1 Mutations

Although mutations in *SOD1* account for a minority of ALS cases, their discovery represents a big step in ALS research, as it allowed the generation of the first murine model (Gurney et al., 1994) and paved the way for crucial pathophysiologic and therapeutic investigations. The exact mechanisms by which *SOD1* mutations lead to motor neuron degeneration in ALS are not fully understood, but several lines of evidence suggest that a key factor is the accumulation of misfolded or aggregated SOD1 protein within motor neurons (Silverman et al., 2016). This can lead to a range of cellular abnormalities, including mitochondrial dysfunction, oxidative stress, altered axonal transport, and activation of inflammatory pathways. Interestingly, misfolded SOD1 pathology has also been described in non-*SOD1* sporadic ALS cases (Paré et al., 2018), but it may not accurately reflect the underlying pathological mechanisms, limiting the generalizability of SOD1 models to sporadic and other inherited forms of ALS (Mackenzie et al., 2007).

One of the key mechanisms involved in *SOD1*-ALS pathology is undoubtedly related to oxidative stress. SOD1 is an important antioxidant enzyme that helps protect cells from damage caused by reactive oxygen species. In ALS, *SOD1* mutations can lead to reduced enzymatic activity and increased reactive oxygen species accumulation, resulting in damage to proteins and lipids, leading to motor neuron degeneration. Therefore, it has been shown that SOD1 interacts with proteins involved in mitochondrial function and transport, leading to mitochondrial abnormalities and reduced energy production. SOD1 has also been implicated in aberrant protein aggregation, including interactions with other disease-associated proteins such as TDP-43 and FUS, disrupting cellular function and causing toxicity. Finally, *SOD1* mutations can activate inflammatory pathways in the central nervous system, leading to the release of pro-inflammatory cytokines and chemokines, resulting in neuroinflammation, a well-established hallmark of ALS pathology.

Overall, although it has been demonstrated that SOD1 interacts with multiple cellular pathways relevant to ALS mechanisms (Kaur et al., 2016), critical questions remain unanswered, including the regulation of *SOD1* transcription and the exact interaction of SOD1 in DNA/RNA metabolism, protein misfolding, and aggregation (Pansarasa et al., 2018).

Superoxide Dismutase 1-Amyotrophic Lateral Sclerosis Genotype-Phenotype Correlation

Mutations in *SOD1* represent the second most common cause of genetic ALS, accounting for approximately 12%–20% of familial and 1%–2% of sporadic ALS (Marangi and Traynor, 2015). The *SOD1*-ALS phenotype has traditionally been

characterized by a spinal onset (Connolly et al., 2020) with predominantly lower motor neuron signs and rare bulbar involvement (Opie-Martin et al., 2022). Upper motor neuron manifestations have been reported in patients with various *SOD1* mutations as confirmed by a systematic review (Connolly et al., 2020). As the mutation sites are constantly being discovered, literature has reported various clinical phenotypes among family members and cases, suggesting a complex genotype-phenotype relationship between *SOD1* and ALS phenotype, closely dependent upon the specific mutation (Connolly et al., 2020).

Considering the complexity of recent advancements, it seems more appropriate to consider the disease trajectory starting from each pathogenic variant, ranging from rapid forms due to dominant A5V mutation to slower progressions linked to recessive D91A mutation. In fact, only a scarcity of *SOD1* variants differentially influenced survival, with about one-third of these variants appearing to be protective, extending overall survival (Opie-Martin et al., 2022). The reasons behind this wide heterogeneity remain to be explained. Several factors have been implicated in the literature, including the effect of the mutation on the stability of SOD1 protein, the emergence of toxic species or folding intermediates as a source of cytotoxic conformations (Berdyński et al., 2022). Additionally, the heterogeneity among families with the same mutation supports the hypothesis that different mechanisms, including genetic and epigenetic modulators, along with external factors, may also influence the presentation and clinical course of ALS.

Extramotor Involvement in Superoxide Dismutase 1-Amyotrophic Lateral Sclerosis

As with other ALS-related genes, extramotor neurological involvement has been described for *SOD1*-ALS patients. One mechanism responsible for the extramotor symptoms in *SOD1*-ALS patients could reside in the prion properties of SOD1 (Ayers et al., 2016), as recently demonstrated by the transfer of both wild-type and mutant SOD1 between neuron and glial cells (Gosset et al., 2022). Considering this pathogenetic backbone, we here examine the literature data on reported extra-motor involvements in the *SOD1*-ALS subpopulation.

From a clinical perspective, the phenotypic spectrum of *SOD1*-ALS cases has been greatly expanded in recent years. The initial descriptions came from a large Scandinavian series of families harboring *SOD1* mutations (Andersen, 1997), demonstrating signs of autonomic, bladder, cerebellar, and/or sensory involvement. Later, Bernard et al. (2020) described a large French *SOD1*-ALS population with polymorphic clinical features, including sensory signs, vocal cord impairment, neurogenic bladder, and facial diplegia. The latest data from an Italian cohort have confirmed the high heterogeneity of clinical manifestations in *SOD1*-ALS (ataxia with cognitive impairment and ALS) at the onset of the disease (Gagliardi et al., 2023). More recently, the first description of human *SOD1* deficiency by Park et al. in 2019 has added another piece to the puzzle: the complete absence of SOD1 activity from the homozygous truncating *SOD1* variant resulted in a severe phenotype characterized by tetraspasticity and hyperreflexia, reflecting upper motor neuron involvement, along with ataxia, muscle hypotonia and severe psychomotor retardation in a young child. Interestingly, this phenotype exhibits distinct similarities (tremor, reduced muscle mass, and motor axonopathy) with the presentation of total *SOD1*-knockout mice (Sakellariou et al., 2018). It is worth noting that a pure overlap between myopathic and neurogenic forms has been described (Tasca et al., 2020), reporting a case of *SOD1*-ALS associated with the D12Y variant, which includes a predominant lower motor neuron form with concomitant distal myopathy, confirmed by MRI and muscle pathology alterations with rimmed vacuoles. Finally, the traditional view of intact cognition in *SOD1*-ALS patients has been recently challenged, with literature reporting frontal lobe vulnerability in ALS patients carrying different *SOD1* mutations (Martinelli et al., 2023). In particular, in *SOD1*-ALS patients, the most specific characteristics of cognitive impairment fall within the ALS-fronto-temporal-dementia (ALS-FTD) spectrum, mainly involving behavioral symptoms with several exceptions including abnormal off-key liquoral analysis consistent with Alzheimer's disease biomarker profile (Müller et al., 2018), hypothalamus dysfunction (Nakamura et al., 2015), and Korsakoff syndrome (Perrone et al., 2018).

Histopathological features related to extramotor involvement in superoxide dismutase 1-amyotrophic lateral sclerosis

In the literature, several relevant histopathological characteristics for *SOD1*-ALS patients have been reported, being associated with different *SOD1* mutations and phenotypes (**Additional Table 1**).

For what concerns the involvement of motor structures, it's been reported the typical degeneration of the corticospinal tract and the loss of lower motor neurons in the anterior horns of the spinal cord, with rare signs of degeneration of pyramidal and cortical structures. Interestingly, alongside these typical findings of motorneuron degeneration, authors reported several signs of involvement of the sensitive system (including dorsal column, spinocerebellar tract, Clarke's column), also in the presence of a classic ALS phenotype and independently from the mutations underlying (Hideshima et al., 2020). Moreover, various combinations of degenerative lesions in other central nervous system structures have been described, including basal ganglia and brainstem nuclei (Orrell et al., 1995), cerebellar system (Takehisa et al., 2001), hypothalamus (Nakamura et al., 2015), neocortical and limbic system (Nakamura et al., 2015).

Histochemical investigations revealed mainly SOD1-immunopositive Lewy body–like hyaline inclusions and aggregation of neurofilaments in motor neurons. Intriguingly, authors reported also pathological signs of degeneration (hyaline inclusions similar to Lewy bodies) in non-motor neurons, including astrocytes (Hineno et al., 2012), and in non-motor systems (Onufrowicz nucleus, Clarke's nucleus, intermediolateral nucleus, posterior gray horn of the spinal cord, in the periaqueductal gray matter, nucleus raphe dorsalis, locus ceruleus, trigeminal motor nucleus, vestibular

nucleus, dorsal vagal nucleus, hypoglossal nucleus, and reticular formation of the brain stem) (Suzuki et al., 2011).

Sensory disturbances

Focusing on the *SOD1*-ALS population, our literature research reveals a significant number of sensory disturbances. The most commonly described symptoms are paraesthesia, dysesthesia, and numbness, but reduced vibration sense and impaired pinprick sensation are also reported (for complete details, see **Additional Table 2**). Notably, there is a case reported by Kostrzewa et al. (1996) of a patient with a long history of symptoms attributable to sensory neuropathy occurring 17 years prior to the diagnosis of ALS. Interestingly, Marjanović et al. (2017) described a large family affected by the L145F *SOD1* mutation, with eleven components presenting with sensitive symptoms. It is noteworthy that we observed the classic phenotype was more frequently associated with sensory symptoms among *SOD1*-ALS patients, while bulbar or respiratory onset was not clearly reported. Consequently, unlike other extramotor involvements, we may suggest a higher mean survival time, although data interpretation is challenging due to high variability and different data collection methods. Among the 40 cases of *SOD1*-ALS with sensory involvement, three patients had a heterozygotic D91A mutation, and one patient had a homozygotic D91A mutation (Marjanović et al., 2017). Consistently, Gellera et al. (2001) reported that neurophysiological evaluation revealed alterations of peripheral sensory system (reduced sensory action potential amplitude), even in the presence of normal sensation, in a patient with homozygotic D91A mutation. Surprisingly, the H47R *SOD1* mutation was separately reported (Østern et al., 2012; Luo et al., 2022) in patients with a clinical presentation consistent with hereditary motor-sensory neuropathy (Luo et al., 2022), suggesting an effect of the *SOD1* mutation on the normal function of both motor and sensory peripheral nerves, although its pathogenetic role in these cases remains unclear.

Concomitantly, a large number of experiments on animal models support the idea of sensory involvement resulting from *SOD1* mutations (Rubio et al., 2016, 2022; Sassone et al., 2016; Taiana et al., 2016; Seki et al., 2019). Rubio et al. (2016) described a loss of sensory axons in the footpads of *SOD1* G93A mice, even in the presymptomatic stage of the disease, and more recently the same group finely characterized the peripheral sensory involvement, detecting a reduction in the intraepidermal nerve fibers density and sweat glands innervation; finally, the authors frame the picture as a distal axonopathy, as the loss or failure to growth involves of the distal portion of sensory axons while preserving the corresponding neuronal bodies (Rubio et al., 2022).

In the whole ALS population sensory involvement is not uncommon, with up to 20% of ALS patients reporting sensory complaints (Hammad et al., 2007) while in *SOD1*-ALS cases a precise percentage has not been assessed, along with several sensitive neurophysiological abnormalities (Hammad et al., 2007; Pugdahl et al., 2008). From a pathological point of view, studies have demonstrated a mild reduction of the number of large nerve fibers (Hammad et al., 2007) and involvement of the spinocerebellar pathway (Clarke's column) in ALS (Turner and Swash, 2015), similarly to the histopathological findings in SOD1-ALS cases (please refer to the previous paragraph).

Urinary/bladder involvement

Several single cases or case series have reported urinary involvement in *SOD1*-ALS patients, most commonly associated with detrusor hyperactivity, urgency, or urinary incontinence. To the best of our knowledge, urodynamic studies have been rarely reported, pointing out a neurogenic bladder with an overactive detrusor type or uninhibited bladder, along with atonic bladder (Kawata et al., 1997; Shimizu et al., 2000; Hayashi et al., 2016). The first report came from Kawata et al. (1997) describing a Japanese familial case of juvenile-onset *SOD1*-ALS with the G94S mutation, which showed a long disease duration and the development of various extra-motor symptoms, including urinary urgency. Hineno et al. (2012) described a large family with 10 *SOD1*-ALS patients carrying the L107V mutation, many of whom developed urinary symptoms described as an overactive bladder as well as urinary retention, with high variability in age at onset and survival. Other cases and case series of *SOD1*-ALS patients, both familial and sporadic, have been reported in Japan, Spain, and France (Shimizu et al., 2000; Gamez et al., 2006; Nakamura et al., 2014; Sakamoto et al., 2014; Hayashi et al., 2016; Taieb et al., 2017), with further details available in **Additional Table 3**. Battistini et al. (2005) described the case of a 53-years-old Tuscan patient with familial *SOD1*-ALS due to the G42S mutation, characterized by an aggressive phenotype and a short disease course, during which he developed urinary disturbances along with sexual dysfunction and cognitive and behavioral symptoms such as disinhibition, visual hallucination, and confusion. However, with the exception of rare cases, the vast majority of the cases described had a disease duration above average, and none of them presented a *SOD1* mutation known to be associated with a rapid progression, suggesting that urinary involvement might occur mainly later in the disease course.

Commonly, incontinence and urinary retention are not considered a classic manifestation in patients with ALS, being often attributed to the use of muscle relaxants and anticholinergic medications or the patient's motor impairments (Swinnen and Robberecht, 2014). However, bladder symptoms are present in the ALS population, reaching up to 25% after diagnosis (Samara et al., 2021). Then, urodynamic studies have shown that these symptoms are caused by a combination of an overactive detrusor muscle and a non-relaxing sphincter (Arlandis et al., 2017), as described in *SOD1*-ALS patients. Interestingly, the histopathological findings confirm the involvement of Onuf's nucleus in patients with ALS with different clinical syndromes, more frequently in cases with pyramidal tract involvement (Bergmann et al., 1995), while in *SOD1*-ALS cases the classic phenotype was more represented.

Extrapyramidal symptoms

So far, few cases of movement disorders in *SOD1*-ALS patients have been reported in the literature (Andersen et al., 1996; Lopate et al., 2010; Yasser et al., 2010; Kacem et al., 2012; Ioannides et al., 2016). In an extensive cohort

study by Andersen et al. (1996), which included 36 *SOD1*-ALS patients with a biallelic D91A variant, two subjects showed mild dysmetria in the arms along with UMN and LMN signs. However, no further clinical information was provided (Andersen et al., 1996). Subsequently, rare cases of cerebellar ataxia associated with *SOD1* mutations have been reported in the literature (Lopate et al., 2010; Yasser et al., 2010), indicating that FALS associated with *SOD1* mutations may have cerebellar features. It is also interesting to note that in the same study, six relatives of the D91A families were affected by Parkinson's disease (PD) but only four PD relatives underwent genetic screening, showing a heterozygous (n = 2) or homozygous wild-type allele (n = 2) (Andersen et al., 1996). Kacem et al. (2012) also reported a patient with a family history of autosomal dominant ALS, who developed early onset levodopa-responsive parkinsonism associated with an intronic mutation (Intron IV, c.358 – 304C > G*) in the SOD1 gene without involvement of motor neurons.

These findings could be even more impactful considering that oxidative stress reactions contribute to PD pathogenesis, and superoxide dismutases like SOD1 can potentially play a role in PD pathogenesis by detoxifying superoxide radicals (Farin et al., 2001). This had been confirmed by a subsequent case-control study that assessed potential associations of gene polymorphisms in *SOD1*, *SOD2* (encoding Manganese-SOD), and *SOD3* (encoding extracellular-SOD) with PD susceptibility (Liu et al., 2019). The results of this study indicated that individuals carrying the AG or GG genotype had a much higher risk of PD compared to those with the corresponding AA genotypes, and carriers of the G allele had a higher risk than carriers of the A allele at the single nucleotide polymorphism (rs2070424 A/G) in *SOD1*, which enhances genetic susceptibility to PD (Liu et al., 2019). Looking at the general ALS population, extrapyramidal features have been also reported (Gilbert et al., 2010), although they are not frequent and can be overshadowed by muscle impairment. ALS associated with PD, also known as ALS-PD complex, is very rare and is characterized by simultaneous or subsequent motor and extramotor involvement (Gilbert et al., 2010). Mild extrapyramidal features have been reported more frequently in ALS patients (5%–15%) (Manno et al., 2013) with some studies also highlighting substantia nigra and striatum degeneration at autopsy (Urso et al., 2022). For what concerns the genetic forms of ALS, an overlap between Parkinsonian features and ALS has been observed more frequently within the spectrum of ALS due to *C9ORF72* expansion, combined with dementia (Origone et al., 2013), cerebellar abnormalities, autonomic dysfunction, and Huntington's disease (Hensman Moss et al., 2014) or *TARDBP* mutation (Chiò et al., 2011). Of course, the incidence of parkinsonism in *SOD1*-ALS patients is lower compared to patients with *TARDBP* mutations. The clinical manifestations of *TARDBP* mutations range from complex ALS phenotypes to ALS-FTD (Arai et al., 2006), both of which can be associated with Parkinsonian features (Tiloca et al., 2022). This may be related to the recent observation of decreased parkin protein in TDP-43 proteinopathies (Polymenidou et al., 2011; Lagier-Tourenne et al., 2012). Furthermore, the possible molecular interaction between α-synuclein, a key protein involved in PD pathology, and SOD1 have been evaluated through multiple studies, in both hSOD1G93A transgenic mice and patient brain tissue, finding their mutual aggregational properties, supporting the hypothesis that α-synuclein in ALS may play a significant role in the pathogenesis of ALS (Takei et al., 2013; Helferich et al., 2015). In particular, a protein-fragment complementation approach has revealed that α-synuclein and SOD1 physically interact in living cells, human erythrocytes, and mouse brain tissue (Helferich et al., 2015). Additionally, disease-related mutations in α-synuclein (A30P, A53T) and *SOD1* (G86R, G94A) have altered the binding of α-synuclein to SOD1, leading to α-synuclein-induced acceleration of SOD1 oligomerization independent of SOD1 activity (Helferich et al., 2015).

Interestingly, Lopate et al. (2010) described a case of choreodystonia associated with an I114T mutation in the SOD1 gene. The choreic and dystonic movements were widespread, persistent, and appeared at the age of 69 years, and were not associated with a sensory trick. Specifically, chorea initially appeared in the upper limbs and then spread extensively. No information regarding pharmacological treatment for involuntary movements was reported by the authors (Lopate et al., 2010). Ioannides et al. (2016) further described a novel SOD1 mutation, G142R, causing motor neuron disease with prominent premorbid cramps and spasms. Interestingly, one of the patients had a long history of dystonic spasms in the lower limbs worsened by exercise, without any sensory tricks, leading to the onset of ALS (Ioannides et al., 2016).

Vocal cord palsy and facial-onset sensory and motor neuropathy

In *SOD1*-ALS patients, ten cases of vocal cord palsy have been described, with various *SOD1* mutations associated and high variability in age at onset (Tan et al., 2004; Fukae et al., 2005; Salameh et al., 2009; Hermann et al., 2011; Origone et al., 2012; Capece et al., 2021; Yogakanthi et al., 2021; **Additional Table 4**). Six of these patients presented with a bulbar phenotype at the onset of the disease. When specified, in four patients bilateral vocal cord palsy was present, while in three cases the paralysis was unilateral. In all reported cases, with the exception of the patient with the homozygotic D91A mutation, the time from onset to death or tracheostomy was very short (range 11–20 months), which aligns with the worse prognosis observed in bulbar onset cases and may suggest the role of vocal cord involvement as a prognostic factor. Facial-onset sensory and motor neuropathy (FOSMN) is a syndrome commonly characterized by paraesthesia and numbness in the region of trigeminal innervation followed by bulbar symptoms, muscle weakness, atrophy, fasciculations and sensory involvement in other limbs, with a long continuously progressive disease course. Dalla Bella et al. (2014) described an Italian sporadic patient with bulbar impairment, sensitive onset, and subsequent bulbar involvement (compatible with the diagnosis of FOSMN), whose genetic testing revealed a D91A substitution in the *SOD1* gene.

Blood pressure regulation impairment – Autonomic impairment

Concerning the *SOD1*-ALS population, literature reports indicate three patients with prominent blood pressure

regulation disorders, as reported in **Additional Table 5**. The Japanese patient described by Kawata et al. (1997) experienced blood pressure fluctuations with hypertensive spikes and nocturnal drops, along with sensory and urinary dysfunctions. Shimizu et al. (2000) described another young sporadic *SOD1*-ALS patient carrying the V119L mutation who suffered from orthostatic hypotension, nocturnal hypotension, and atonic bladder. Hayashi et al. (2016) reported another familial *SOD1*-ALS patient with orthostatic hypotension. Interestingly, the latter two patients also reported having ophthalmoplegia (Shimizu et al., 2000; Hayashi et al., 2016). All the described patients also exhibited urinary symptoms, suggesting that the poor blood pressure control observed in these *SOD1*-ALS patients may be indicative of a broader dysautonomic impairment, as recognized in transgenic mice carrying an *SOD1* (G93A) mutation (Kandinov et al., 2011).

Autonomic abnormalities are not rare in the general ALS population, with mainly urinary and intestinal problems (McCombe et al., 2017). Other autonomic alterations have been reported, such as abnormal heart rate variability (Merico and Cavinato, 2011), and sudomotor dysfunction (Beck et al., 2002; Piccione et al., 2015). Autonomic dysfunctions are weighted differently by the determination method, being more detectable with the application of fine quantitative measures (Weise et al., 2022), limiting the comparison between different studies and cohorts.

Conclusions

A growing body of evidence now suggests that ALS should be seen as a multisystem disease with early and frequent impacts on cognition, behavior, sleep, pain, and fatigue, with corresponding pathobiological basis (Mahoney et al., 2021). The full impact of non-motor dysfunction continues to be established but there is now sufficient evidence that the presence of non-motor symptoms influences overall survival in ALS, with up to 80% reporting non-motor symptoms (Mahoney et al., 2021). In this context, several *SOD1* mutations have been linked with extramotor features which may represent the result of a complex interplay between differentially affected tissues, considering the ubiquitous expression of *SOD1*. The unpredictable expression of *SOD1* mutations highlights that *SOD1* testing should be performed in all atypical motor neuron diseases, especially in cases with the absence of upper motor neuron signs or with SMA-like presentation (Bernard et al., 2020).

Although limited by the non-systematic nature of the review, our research revealed a high proportion of sensitive impairment in *SOD1*-ALS, being associated with prevalent LMN involvement and longer survival. Then, dysautonomic involvement has been reported, mainly with urinary symptoms more frequently described in long-lasting forms of ALS. Finally, a relatively high number of vocal cord palsy has been surprisingly reported in *SOD1*-ALS, with predominant bulbar phenotype and short survival.

Extra-motor neuron features in ALS are emerging as clinically highly impactful in patients' quality of life and disease progression (McCombe et al., 2017). Their thorough investigations are proving critical not only for providing important insights into common mechanisms of pathogenesis, but also by offering the opportunity for direct samplings, representing potentially exploitable biomarkers to follow the response to incoming personalized therapy for *SOD1*-ALS patients.

In turn, widening the genotype-phenotype among the different mutations in *SOD1*-ALS cases could be helpful towards a deeper comprehension of *SOD1* pathomechanism and could prompt targeted genetic testing.

These considerations gain even more value in light of the recent therapeutic strategies for *SOD1*-ALS (Miller et al., 2022), whose impact on extramotor symptoms should be assessed, as long as the proper interpretation of the role of *SOD1* mutation as a key point functional to predict therapeutic efficacy.

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Conflicts of interest: *The authors declare no conflicts of interest.*

Data availability statement: *All relevant data are within the paper and its Additional files.*

Additional files:

Additional Table 1: *Histopathological findings in SOD1-ALS patients.*

Additional Table 2: *Sensory involvement in SOD1-ALS.*

Additional Table 3: *Urinary involvement in SOD1-ALS.*

Additional Table 4: *Vocal cord palsy in SOD1-ALS.*

Additional Table 5: *Dysautonomic findings in SOD1-ALS.*

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