Motor neurone diseases

PP4087

TARDBP mutation mimics a distal motor neuropathy in a Sardinian patient
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Introduction: TARDBP-related Amyotrophic Lateral Sclerosis (ALS) patients present an adult-onset, autosomal dominant clinically typical form of ALS. TARDBP mutations are also observed in both ALS-Fronto Temporal Dementia (FTD) and pure FTD cases. Since first TARDBP mutations were reported in familial ALS cases in 2008, over 40 mutations have been identified in several populations of different geographic origin. Here we report an atypical case of TARDBP-associated ALS patient, coming from Sardinia, an Italian island historically genetically segregated and distinct from other European populations.

Methods: A 50-years-old man came to our attention for a 10-year story of slowly progressive mild symmetrical limb distal hyposthenia and amyotrophy with cramps and fasciculation. No upper motor neuron sign either sensitive impairment was present. Electrophysiological examinations were consistent with second motor neurons damage. A psychiatric history of bipolar disorder was present without cognitive impairment. No family history of neuromuscular disorders.

Results: Genetic analysis revealed that the patient was carrying in heterozygosis the c.1144G->A (p.A382T) pathogenic missense mutation of the TARDBP gene.

Conclusions: TARDBP p.A382T missense mutation accounts for approximately one-third of all ALS Sardinian cases. Despite a quite heterogeneous spectrum of resulting phenotypes, the flail arm variant of ALS occur with greater than expected frequency in these patients, although clinical presentation may also include forms of parkinsonism and FTD. To our knowledge, this is the first report of a distal motor neuropathies-like syndrome associated with this mutation.

Disclosure: Nothing to disclose

PP4088

Amyotrophic lateral sclerosis – clinical signs and epidemiology of the last 15 years in entre Douro e Vouga – Portugal
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Introduction: Estimated incidence of Amyotrophic Lateral Sclerosis (ALS) in Europe is 2/100,000hab/year, and prevalence 3-6/100.000hab/year, with males being affected more frequently (M:F=1.5:1). The major risk factor is age, and median survival about 3yrs. Poor prognosis has been ascribed to an early diagnosis, late beginning, female gender and bulbar onset. Only 20% of cases begin as progressive bulbar palsy (PBP).

Methods: Clinical and epidemiological characterization of ALS patients followed in our centre between January/1999 and December/2013, through retrospective analysis of their clinical registrations.

Results: 55 patients were identified, rendering an incidence of 1.1/100,000hab/year and prevalence of 5.3/100,000hab. Median age of onset was 65 years and median survival was 38 months. A shorter survival was associated with initial bulbar signs and shorter time to diagnosis. Males were 1.4 fold times more affected than women, with women displaying a later onset (p=0.01). Initial bulbar signs were also more frequent among women, with an overall incidence of 44% (36.4% as PBP). Following multivariate analysis, physiotherapy, age of onset, non-invasive ventilation and gastrostomy didn’t show to be associated with longer survival.

Conclusions: This study corroborates the clinicians’ impression of an unusual high prevalence of premature bulbar signs in our population, what proved to be associated, as previously reported in literature, to a shorter survival. Prospective studies will be needed to prove the effect of other variables upon survival and prognosis.

Disclosure: Nothing to disclose
PP4089

A case of amyotrophic lateral sclerosis associated with distal agenesis of an upper limb, hyperinsulinaemic hypoglycaemia, and hypocupraemia

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Introduction: We describe a case of motor neuron disease accompanied by congenital skeletal abnormalities, hyperinsulinaemia and hypocupraemia.

Methods: Description of the patient: A 47-year-old Caucasian man presented to our Institute with a 20-month history of progressive distal right upper limb weakness and muscular atrophy. He also had a congenital somatic defect consisting of agenesis of the left forearm and hand, and had suffered for 10 years from episodes of hypoglycaemia.

Results: On neurologic examination, distally-predominant weakness of the right upper limb was present, accompanied by fasciculations of the tongue and of the four limbs with generalized hyperreflexia. This pattern, as well as the electromyographic examination, was consistent with the diagnosis of amyotrophic lateral sclerosis (ALS). Radiographs of the skeleton showed hypogenesis of the phalanges of the right hand and of the feet in adjunct to the obvious defect of the left upper limb. Blood tests demonstrated hypoglycaemia with a high insulin level, suggesting the presence of an insulinoma which was, however, not found by computed tomography and endoscopic ultrasonography. Reduced serum levels of both copper and ceruloplasmin were also found, with a normal urinary copper excretion.

Conclusions: To our knowledge, the association of ALS with such skeletal developmental defects and endocrine-metabolic abnormalities has not been previously described. As it is statistically unlikely that such anomalies coexist by chance, we consider that they could represent a genetic syndrome or, alternatively, be consequence of a pathogenic insult occurred during embryogenesis.

Disclosure: Nothing to disclose
**PP4090**

**A case of bulbar-onset amyotrophic lateral sclerosis associated with Alzheimer’s disease**

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**Introduction:** We report a case of bulbar-onset amyotrophic lateral sclerosis (ALS) associated with Alzheimer’s disease (AD).

**Methods:** Description of the patient: A 76-year-old woman insidiously developed forgetfulness and difficulty in performing activities of daily living. After two months, dysarthria arose, followed by dysphagia. The symptoms progressed over time, and the patient came to our attention 14 months after the onset of the cognitive problems.

**Results:** On neurologic examination, the patient was severely dysarthric, with tongue atrophy and fasciculations and a brisk jaw jerk. There was very mild weakness of right biceps brachii and wrist flexors. Deep tendon reflexes were normal in the upper limbs and reduced in the lower limbs. Electromyographic examination was consistent with a diagnosis of ALS. Neuropsychological testing demonstrated moderate deterioration of multiple cognitive functions. Imaging studies showed global cerebral atrophy and reduced glucose uptake in the temporal and occipital lobes. Positron emission tomography with florbetapir disclosed pathological brain deposition of amyloid, while cerebrospinal fluid analysis demonstrated reduced A-beta 1-42 and elevated tau and phospho-tau. These findings are consistent with the diagnosis of Alzheimer’s disease.

**Conclusions:** This case illustrates that when ALS is accompanied by dementia, the cognitive impairment is not necessarily due to frontotemporal lobar degeneration as most frequently reported, but can occasionally be caused by AD. More intriguingly, the almost simultaneous onset of the two diseases leads us to consider the possibility that AD pathology may underlie not only dementia but also ALS.

**Disclosure:** Nothing to disclose

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**PP4091**

**Adult-onset case of Brown-Vialetto-Van-Laere syndrome with SLC52A3 mutation**

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**Introduction:** Brown-Vialetto-Van Laere syndrome (BVVLS) is a rare neurological disorder characterized by childhood onset motor neuron involvement, sensorineural deafness and ponto-bulbar palsy. Recently, mutations in SLC52A3, coding for riboflavin transporter 2, have been identified as the molecular basis for most of the individuals with BVVLS, providing a unique opportunity for treatment. Majority of the patients with genetically proven BVVLS in the literature manifested in childhood and adult onset disease is considered as atypical.

**Methods:** Case presentation with clinical, electrophysiological and whole genome sequencing data.

**Results:** 41-years-old female patient presented first with difficulty in gait about 10 years ago. Five years later, she developed dysphagia and dysarthria. Symptoms were slowly progressive. She was on riluzole therapy when she was first seen in our clinic. Her history revealed mild loss of hearing and prominent loss of weight at about age of 25. She is between 35-40kg since then. Electromyographic studies showed mildly active, chronic, diffuse lower motor neuron involvement. BVVLS was suspected and genome wide analysis and sanger sequencing was done revealing homozygous p.P267L mutation in SLC52A3 gene. Riboflavin treatment has been started thereafter.

**Conclusions:** Although very rare, BVVLS may first present at adulthood. As riboflavin treatment, at least, is shown to halt progression of disease, it is important to consider BVVLS in differential diagnosis of patients with motor neuron disease.

**Disclosure:** Nothing to disclose
**PP4092**

**Bee venom effects on UPS system in an ALS model**

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**Introduction:** Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that results from a progressive loss of motor neurons. Familial ALS (fALS) is caused by missense mutations in Cu, Zn-superoxide dismutase 1 (SOD1) that frequently result in the accumulation of mutant-protein aggregates that are associated with impairments in the ubiquitin-proteasome system (UPS). UPS impairment has been implicated in many neurological disorders. Bee venom (BV) extracted from honey bees has been used as a traditional medicine for treating inflammatory diseases and has been shown to attenuate the neuro-inflammatory events that occur in a symptomatic ALS animal model.

**Methods:** NSC34 cells were transiently transfected with a WT or G85R hSOD1-GFP construct for 24hrs and then stimulated with 2.5μg/ml BV for 24hrs. To determine whether a SOD1 mutation affects UPS function in NSC34 cells, we examined proteasome activity and performed Western blotting and immunofluorescence using specific antibodies, such as anti-misfolded SOD1, anti-ubiquitin, anti-GRP78, anti-LC3, and anti-ISG15 antibodies.

**Results:** We found that GFP-hSOD1G85R overexpression induced SOD1 inclusions and reduced proteasome activity compared with the overexpression of GFP alone in NSC34 motor neuronal cells. In addition, we also observed that BV treatment restored proteasome activity and reduced the accumulation of ubiquitinated and misfolded SOD1 in GFP-hSOD1G85R-overexpressing NSC34 motor neuronal cells. However, BV treatment did not activate the autophagic pathway in these cells.

**Conclusions:** Our findings suggest that BV may rescue the impairment of the UPS in ALS models.

**Disclosure:** Nothing to disclose

**PP4093**

**The effects of sacolopendra subspinipes mutilans on neuroinflammation in symptomatic ALS mice**

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**PP4094**

**Tandem mass spectrometry resting and exercise-related plasma levels of C6 and C12 bi-carboxylic carnitines in ALS: a putative new disease biomarker**

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**PP4095**

**Case report of spinal muscular atrophy (autosomal dominant type of inheritance?)**

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**PP4096**

**Pattern difference of dissociated hand muscle atrophy in upper limb-onset amyotrophic lateral sclerosis, progressive muscular atrophy, brachial amyotrophic diplegia, and Hirayama disease**

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**PP4097**

**In silico analysis of the SOD1 gene mutations**

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**PP4098**

**Inflammatory reactions in ALS: possible effects on clinical symptoms and laboratory parameters by treatment**

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**PP4099**

**Blood pro- and antioxidant system in patients with motor neuron diseases at different progression rates**

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**PP4100**

**Disruption of deglutition and respiration interaction is caused to the dysphagia in ALS patients**

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**PP4101**

**Abstract withdrawn**