Dementia with Lewy body (DLB) is one of the neurocognitive disorders pathologically caused by deposition of the alpha-synuclein in the brain predominantly in the limbic system, neocortex and substantia nigra (Kim et al., 2014). Alpha-synuclein is an amino acid found in the presynaptic end of the neurons and key in the pathogenesis of many neurodegenerative disorders including Lewy body dementia (Kim et al., 2014). These diseases for many years offer therapeutic challenges and currently, there is no specific treatment known to reverse their progression, therefore we sought to discuss alpha synucleins (α-syn) and advances in the treatment of DLB.

CASE PRESENTATION

An 80 years old woman. A known HIV seronegative patient. She presented to our facility with 4 months history of progressive limbs weakness, 2 months of inability to speak well, and 7 days of a cough.
History of presenting illness

The condition started 2 years ago when she developed abnormal behaviours, mainly forgetfulness and visual hallucinations. Many times she had been seeing people walking into her room and others trying to abuse her sexually. Occasionally she could hear her friends calling her name. She had been in and out hospital due to those abnormal behaviours and was managed for psychiatric illness on several occasions with unknown antipsychotic medications. Those behaviours worsen in the last 4 months and had had 4 admissions with a period of 4 months.

About 4 months prior to admission the family noted a progressive weakness of the limbs. The weakness started from the lower limbs, initially problems with sustaining good gait on movement. It kept on worsening till she became bedridden 2 months ago. The family also noted she was unable to use her hands about 2 months ago. They reported that her arms shake all the times, even at rest.

About 2 months ago she also developed difficulties in speaking. It was gradual and slowly progressing over time. It was associated with difficulties in taking in feeds about a week prior to this admission. Then this was followed by a productive cough with whitish sputum.

Because of the weakness, she was put under physiotherapy care about a month prior to admission but no great improvement noted since then.

In the review of the other systems, the family reported a history of on/off constipation over a period of 1 month and progressive lower limbs swelling. Otherwise, she had no history of convulsions, no headaches or bladder/bowel disturbances.

Past Medical, Drugs and Social History

She has a history of hypertension for about 10 years and she has been on and off amlodipine and losartan. She had not been at all on any antihypertensive drug for about 2 months prior to admission. She lives with her daughter.

Physical examination

On examination, she was an elderly lady, lying supine on the bed. She was looking sick but awake. She had no pallor, jaundice or lymphadenopathies. She had lower limbs oedema up to the mid legs. Her blood pressure was 128/60 mmHg; pulse rate was 108 bpm and regular; respiratory rate was 20 b/m and regular; temperature was 37.0°C, and pulse oxygen saturation was 96%.

In the neurology examination, she had open and tracking eyes, she could speak incomprehensive words and localized pain on the sternal rub. Her brainstem reflexes (pupillary and corneal reflexes) were in tack. She had expressionless face however the rest of the cranial nerves examination was limited by her mental state. She had the rigidity of the neck (in all directions), the trunk and all the limbs. She had an increased jaw reflex. All the limbs revealed characteristic lead pipe rigidity with increased reflexes and modest wasting. The sensory and coordination examinations were limited by her mental state. The examination of the neck and the back showed no obvious deformities or tenderness.

The chest examination was limited by her poor respiration effort. However, the rest of the other systems examinations were unremarkable.

Investigations

The laboratory tests showed white cell counts (WBC) of 8.3 ×10⁹/l, haemoglobin (Hb) of 10.2 g/dl, platelets
(PLT) of 276×10⁴/l, blood urea nitrogen (BUN) of 32 mg/dl, and creatinine of 0.7 mg/dl. Other tests revealed Na⁺ of 134.8 mmol/l, K⁺ of 3.27 mmol/l, a random blood sugar of 6.8 mmol/l and urine analysis was negative for nitrite.

The chest radiograph showed features of consolidations at the right lower zone and the computerized tomography (CT) showed normal age-related changes with no areas of hyper/hypodense and no masses. Bedside electrocardiography and echocardiography revealed normal findings.

In summary

We presented an 80 years old, HIV seronegative woman with 2 years history of abnormal behaviours that had been managed for psychiatric illness with unknown medications. She has a 10 years history of hypertension and had been on and off anti-hypertensive medications. She was admitted with progressive limbs weakness, started from lower limbs then involving the upper limbs and trunk over a period of 4 months. She developed difficulties to speak about 2 months prior to admission and later productive cough. Otherwise, she has no history of trauma, convulsions, headaches, or neck pain. On examination, she scored 15/16 of four scores. She had an expressionless face; rigid neck and trunk; and global lead pipe rigidity of all the limbs with hyperreflexia. However no deformities or tenderness at the neck or back. The cranial nerves, sensory, coordination, and chest examinations were limited by her mental state and poor respiratory effort. Subsequently, the brain CT scan revealed normal findings. The chest radiograph showed features of consolidation at the right lower zone.

Our impression was a Lewy body dementia with aspiration pneumonia, global rigidity, dysphagia, and reduced level of consciousness.

Management

We gave her levofloxacin 500 mg od for 5 days and metronidazole 500mg t.d.s for 7 days for the aspiration pneumonitis. We gave bisacodyl 5 mg od every night for 3 days for constipation and physiotherapy was initiated. She was discharged after 5 days of antibiotic therapy with much improvement. She was planned to start the LBD specific therapy from the neurology clinic when she is much better according to the neurologist advice.

DISCUSSION

ALPHA-SYNUCLEIN AND ADVANCES IN THE TREATMENT OF LEWY BODY DEMENTIA AND RELATED DISORDERS.

Many studies have suggested the role of alpha-synuclein in the pathogenesis of many neurodegenerative diseases including dementia with Lewy bodies. These group of disorders is known as alpha-synucleinopathies and are classified based on the appearance of α-syn deposits (Kim et al., 2014). These diseases include dementia with Lewy body (DLB), Parkinson’s disease (PD), Parkinson’s disease dementia (PDD), and multisystem atrophy (MSA) (Valera et al., 2016). Currently, there is no specific therapy to reverse or prevent the progression of these diseases. The recent focus of most researchers is on the drugs that disintegrate or prevent the aggregation of α-syn.

ALPHA-SYNUCLEIN

Alpha-synuclein is a protein composed of 140 amino acids expressed in the presynaptic neurons. The proteins are deposited widely in the brain predominately in the neocortex, thalamus, substantia nigra, hippocampus and cerebellum. It causes varieties of neurodegenerative disorders known as alpha-synucleinopathies. The appearance of alpha-synuclein inclusions in different stains leads to the differentiation of these diseases e.g
Lewy bodies in PD and DLB, axonal spheroids in neuro-axonal dystrophies, and cytoplasmic inclusions in MSA (Spillantini et al., 1997, Gai et al., 1998, Newell et al., 1999).

Structure, functions and pathogenesis

The α-syn protein has 3 distinct domains in its structure. The N-terminal region which contains 11 amino acid repeats; the central hydrophobic region, which plays a major role in aggregations; and the C-terminal region. The α-syn is thought to supply vesicles into mature presynaptic terminals, which is required for the formation of presynaptic neurotransmitters. Studies have shown that SNCA missense mutations increase production of the α-syn fibril. This results into misfolding and aggregations, which is the hallmark of the pathogenesis of Parkinson’s related disorders (Kim et al., 2014). Suppression of α-synuclein protein levels using genetic manipulation methods significantly protected against parkinsonian toxin MPTP/MPP+ -induced toxicity and thereby reduced neuronal damage in both human dopaminergic neuroblastoma cells and free-moving animals (Venda et al., 2010).

Alpha synucleins normally exist as unfold monomer. Three-point mutations (A30P, E46K, and A53T) in alpha-synuclein genes were found to be associated with the development of the alpha-synucleinopathies. Defects in post-translational modification form the hallmark of the pathologic mechanism of alpha synucleins, resulting into aggregations and neurotoxicities (Kim et al., 2014). Overexpressing α-synuclein in neurons inhibits synaptic vesicle exocytosis and reduces the readily releasable and recycling synaptic vesicle pools, and thus reduces neurotransmitter release and this result into major features associated with these diseases (Nemani et al., 2010). Phosphorylation of the serine 129 residues is the most common post-translational pathogenic process and is present in the majority of the cases of DLB. Nitration of some amino acid residues in the alpha synucleins molecule is found to cause aggregation and programmed neural cells death (Kim et al., 2014). This is thought to be accelerated by the increased reactive oxygen species especially in the cases of DLB.

Defects in the alpha synucleins clearance were reported as another mechanism of neurotoxicity in alpha-synucleinopathies. Alpha synucleins are normally broken down by Ubiquitin-proteasome system (UPS) and by autophagy-lysosomes pathway (ALP)(Dehay et al., 2015). Dysfunction in these degradation systems has been associated with the development of Parkinson’s related disorders (Chu et al., 2009).

Recent studies had shown that alpha synucleins deposits can be transmitted from one neuronal cell to another in a progressive fashion, described as prion-like propagation(Li et al., 2008, Guo and Lee, 2014, Desplats et al., 2009).

ADVANCES IN THE TREATMENT OF DLB AND OTHER RELATED DISEASES

Alpha synucleins have gained significance in the recent past mainly due to its presence in most of the neurodegenerative diseases. Studies in the animals and in vitro model have been promising to reverse the phosphorylation of S129 in alpha synucleins. However, this has not yet been translated into clinical trials (Dehay et al., 2015).

Therapies targeting aggregation:

It is mainly the use of immunotherapy, the antibodies against α-syn aggregation. These had been demonstrated in several animal models to be effective in the treatment of Parkinson’s disease and the related disorders (Dehay et al., 2015).

Passive immunotherapy

PRX002:
It is a monoclonal antibody against the alpha synuclein aggregation, which acts on the C-terminal of the protein. In the phase 1 study in which healthy adults were recruited, a good antibodies tolerability was observed. A significant reduction of serum α-syn was demonstrated with no major side effects and hence phase1 trial of PRX002 was regarded as successful (Schenk et al., 2017). The phase 2 trial for PRX002 has already been started.

BIIB054:

It is a human recombinant monoclonal antibody targeting alpha synucleins. The phase 1 randomized preclinical trial evaluating safety, tolerability, pharmacokinetics and immunogenicity in healthy subjects and Parkinson’s patients is currently on the way and the completion of primary data collection is expected to be in November 2017 (https://clinicaltrials.gov/ct2/show/NCT02459886).

Active immunotherapy

AFFITOPE has conducted a successful phase one trial on PD01A vaccine. About half of the patients vaccinated developed alpha synuclein antibody. A good CNS penetration of the vaccine was also observed (http://www.affiris.at/press_releases/PD01A_MJFF_E.pdf). In contrast to passive immunotherapy, it may require fewer injections and take a long time. But it could induce an immune response by formation of polyclonal antibodies (George and Brundin, 2015).

Therapies preventing clumping

NPT-200-11:


We managed our patient’s aspiration pneumonitis and she was planned for a review by the neurologist to strategize her treatment of dementia with Lewy bodies in the outpatients’ clinic. She was discharged in a good condition.

CONCLUSION

Dementia with Lewy bodies like other alpha-synucleinopathies has been under therapeutic evolution. Though traditional treatment strategies hold up to date in our setting and many centers, we sought to highlights the current important updates on treatment of Parkinson’s related disorders. Many drugs companies are sponsoring these preclinical trials especially those on the potential alpha-synuclein-based disease-modifying therapy. Of course, there are many challenges with these agents including the CNS penetration of the immunotherapy, the unknown nature of the good alpha-synuclein and their levels. However, these challenges help to improve validation of biomarkers and therapies. These advances in treatment give a new hope to patients with dementia with Lewy bodies and other related progressive degenerative
About EssaySauce, the student essay site:

EssaySauce.com is a free resource for students, providing thousands of example essays to help them complete their college and university coursework. Students can use our free essays as examples to write their own.

Latest student essays:

- Force to temperature
- Germination and seedling emergence
- Gross primary production, community respiration...
- Leaf area index estimation from allometric ...
- Photosynthesis Lab
- SILICON
- Fossils
- Seaweed
- METHODS OF BUSINESS RESEARCH
Student essay categories:

Business essays
Economics essays
Education essays
Engineering essays
Finance essays
Health
Health essays
History essays
Information technology essays
Law essays
Literature essays
Marketing essays
Music Essays
Photography and arts
Photography and arts essays
Politics
Politics essays
Psychology essays
Religious studies and Theology essays
Science essays
Sociology essays
Zoology essays

Average review:

Overall rating: 0 out of 5 based on 0 reviews.

Q: Is EssaySauce.com free?

Yes! EssaySauce.com is a completely free resource for students. You can view our terms of use here.
Why use Essay Sauce?

The brightest students know that the best way to learn is by example! EssaySauce.com has thousands of great essay examples for students to use as inspiration when writing their own essays.

Is Essay Sauce completely free?

Yes! EssaySauce.com is a completely free resource for students. You can view our terms of use here.