Chapter 2

Rare and Disabling Movement Disorders: An Indian Experience

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Additional information is available at the end of the chapter

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Abstract

Recent decades have seen exciting developments in the field of movement disorders. These include identification of rare clinical syndromes and use of technological advances to understand their pathogenesis. Three such disorders are discussed here. The description of the Uner Tan syndrome from Turkey and surrounding regions provoked research into the controversial field of genetically induced devolution. Such cases with few additional findings have now been described from India. Sepiapterin reductase deficiency is a rare treatable autosomal recessive form of dopa responsive dystonia. Indian literature has recently added five confirmed cases to the international database. Such cases are eminently treatable. Successful application of modern technology in understanding the pathogenesis of progressive neurodegenerative disorder has been highlighted in the section on hereditary spastic paraplegias. Hitherto undescribed subcellular organelle transport defects and their potential rectification with known drugs have been demonstrated raising hopes for their cure.

Keywords: movement disorders, Uner Tan syndrome, neurogenetics, sepiapterin reductase deficiency, hereditary spastic paraplegia, stem cell modelling of HSP

1. Introduction

Movement disorders is a relatively young but fast growing sub-speciality of neurology. Recent developments in the clinical, genetics and treatment aspects of this group of disorders are exciting. The nature of movement disorders seen in India differ from the western cases. The vast population of the country where consanguineous marriages are still prevalent is a source of large number of rare movement disorders. Modern technology including whole genome sequencing has promoted in-depth understanding of such cases. In addition, such rare disorders can lead to physical disability especially in children when they remain undiagnosed and

untreated. This paper highlights selected Indian contributions to such developments with an intention to increase awareness about such rare disorders. Some of them are potentially treatable. The topics discussed here include Uner Tan syndrome, sepiapterin reductase deficiency and hereditary spastic paraplegia.

2. Uner Tan syndrome

In the year 2005, Uner Tan from Turkey discovered and described an autosomal recessive genetic syndrome, at present, recognized as Uner Tan syndrome (UTS), which composed of habitual quadrupedalism, impaired intelligence, primitive language and no conscious experience [1]. The cases described by him had quadrupedal locomotion (Q/L) using two palms and two feet with extended legs. Some of them later developed bipedal locomotion (B/L) although Q/L remained the preferred mode of locomotion. Recently he has described similar cases presenting with infantile hypotonia which disappeared by adolescence to be replaced by quadrupedal locomotion [2]. The cases without infantile hypotonia are now identified as UTS Type I and those associated with infantile hypotonia are identified as UTS Type II cases. Considering the unusual psychomotor behaviour of these cases, resembling that of sub-human primates, Uner Tan proposed the theory of 'genetically induced devolution' to explain the genesis of this syndrome. This theory has been questioned by other researchers [3]. This chapter documents two new families of UTS from India. Additional features of dystonia, which appear with their bipedal locomotion, are highlighted.

2.1. Indian cases of UTS

The present chapter describes clinical and radiological findings in three cases of UTS belonging to two Indian families [4] (**Figure 1**). Both of these families resided in Mantur, a small village belonging to Belagavi district in the state of Karnataka. The village is close to semi urban cities with exposure to modern lifestyle practices. Family A had one female case, whereas Family B had two male cases affected by the syndrome. Autosomal recessive type of transmission was identified in each of the families. There was no history of birth asphyxia, trauma or encephalitis in any of the cases. Haematological and biochemical tests, including serum parathormone, vitamin D3, B-12, copper and ceruloplasmin levels, were measured and found to be within normal limits. The VLDL receptor gene was negative in all the cases. For sake of brevity, the girl belonging to Family A is designated as Case A-1 and the brothers belonging to Family B are designated as Case B-1 (elder) and Case B-2 (younger), respectively.

2.1.1. Case A-1

This girl who was born of post-term pregnancy as a large baby had remained floppy until the age of 5 years. She developed Q/L at the age of 6 years and B/L at the age of 11 years. She had features of severe mental retardation with a MMSE score of 0/30. Speech was absent but she repeatedly mumbled a meaningless word. She responded to few commonly used non-verbal commands. Self-care was poor. Most often she moved using Q/L, but at times attempted walking with a wide-based ataxic bipedal gait. She suffered sleep onset epileptic seizures

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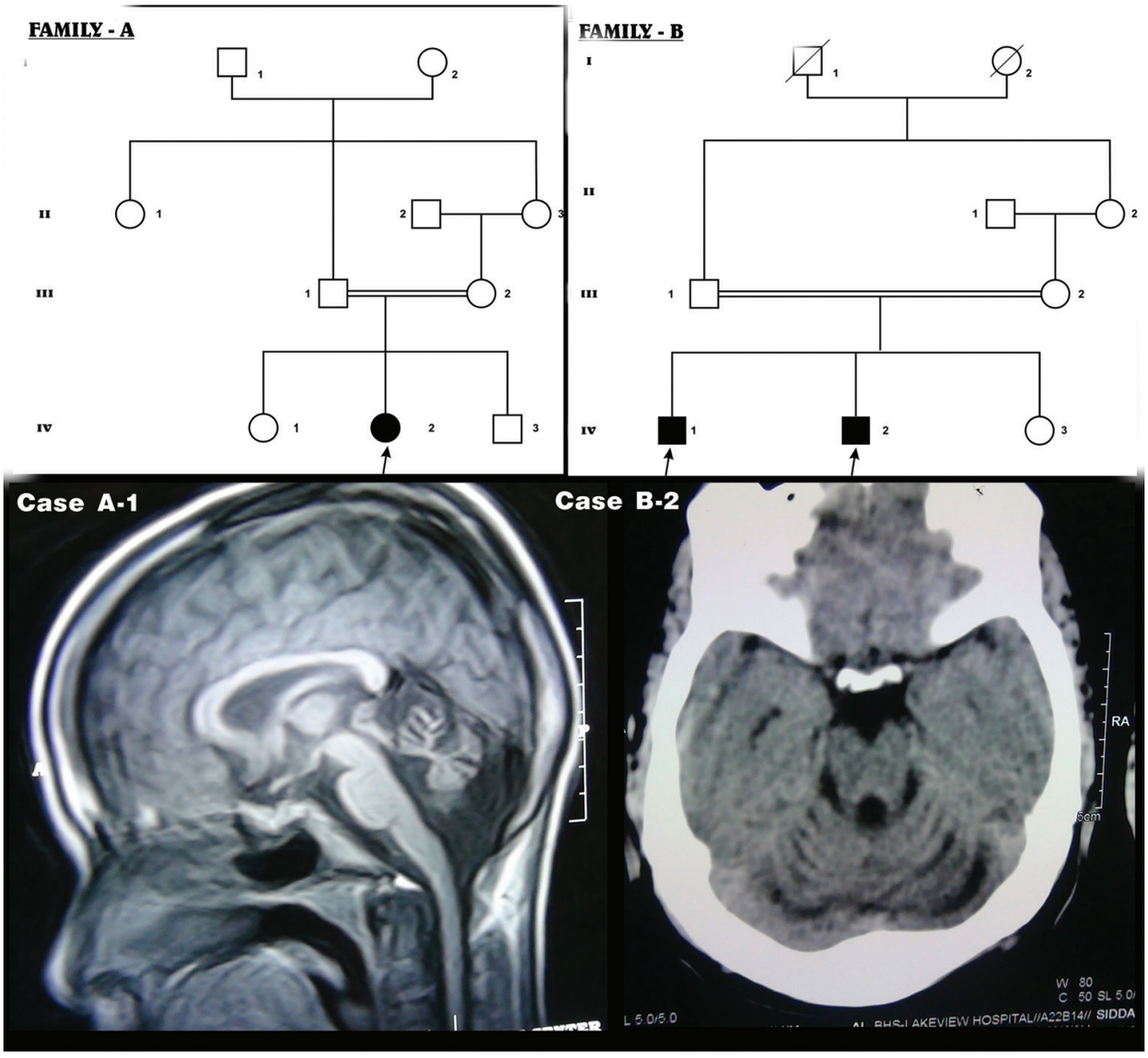

Figure 1. The top section of the figure shows the genogram of Families A and B. The lower section of the figure shows MRI/CT brain images of patients A-1 and B-2, respectively. The images reveal the presence of cerebellar atrophy.

from the age of 18 months, which were partly controlled with phenobarbitone. MRI of the brain revealed moderately severe hypoplasia of the cerebellum including the vermis along with mild cerebral cortical thinning.

2.1.2. Case B-1

This 35-year-old male who was born of full-term normal home delivery had no infantile hypotonia. Features of severe mental retardation were present with no speech but he was able to follow few non-verbal commands. MMSE score was 0/30 and self-care was poor. He exhibited severe autistic behaviour avoiding eye to eye contact with others. He used only Q/L which had appeared at the age of 7 years (**Figure 2**). He never attempted B/L. He could be made to stand with support for few seconds using a wide base support. He suffered rare episodes of generalized tonic-clonic seizures which remained untreated. Neuroimaging was not possible in him.

Figure 2. The figure is a still photography of Case B-1 showing the quadrupedal locomotion. Note the diagonal sequencing of the limbs and the extension of the lower extremities at the knee.

2.1.3. Case B-2

This 30-year-old younger brother of Case B-1 and born of normal home delivery had evidence of severe mental retardation with no speech and MMSE score of 0/30. He exhibited autistic behaviour shunning crowds and often strayed away silently. He had developed Q/L at the age of 7 years and B/L at the age of 25 years. His bipedal gait was wide-based and short-stride but not ataxic. He had camptocormia and almost continuous dystonia abductor posturing of his right arm during bipedal locomotion. Presently, he prefers to move bipedally for most of the time. A CT scan of the head revealed evidence of cerebellar hypoplasia.

2.1.4. Discussion

The diagnosis of UTS was made in these cases based on the presence of the cardinal features of the syndrome as mentioned above.

Most cases reported by Uner Tan resided in remote villages of Turkey having poor communication with the outer world. He proposed that their alienation from outside world,

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low socio-economic status, poor nutrition and poor parental care may be contributing to the causation of the syndrome [1]. In contrast although our cases resided in a village, they were exposed to modern lifestyle practices in view of close proximity to urban settings. These sibs lived protected as members of 'nuclear families', a concept still prevalent in rural India.

In addition to the cardinal features of the syndrome, these patients had (i) microcephaly with facial dysmorphism, (ii) restrictive repetitive behaviours and stereotypies and (iii) poor social interaction. Head circumference in relation to body height measurements mentioned in the table indicates the presence of mild microcephaly in all the cases. While Case A-1 had the feature of repetitive mumbling of a meaningless word, a form of verbal stereotypy, Case B-1 and Case B-2 had extremely shy behaviour avoiding eye to eye contact, social interaction and communication. Dystonic limb posturing was present in cases 2 and 3 during attempted bipedal locomotion.

The pathophysiology of habitual quadrupedalism is unclear. The role of central pattern generators (CPG) present in the cervical and the lumbosacral spinal segments has been discussed in this regard. Reorganization and adaptation of CPG networks is possibly involved in the appearance of human quadrupedal locomotion [5]. Considering the complex balance mechanisms needed for a well-balanced bipedal locomotion, walking on all the four is much easier since the overall base of support of the body is better in the latter type of locomotion [6]. In this regard, the possibility of quadrupedalism appearing as an epiphenomenon secondary to very early onset balance problem cannot be ruled out. The Indian cases were noted to have mild forms of limb dystonia, which became obvious when they attempted bipedal locomotion. In one of his reviews, Uner Tan pointed out that basal ganglia signs were absent [7]. Future studies in UTS may need to incorporate these clinical features to revise our present understanding of this interesting syndrome.

In summary, the clinical observations made in the Indian cases of UTS suggest that components of limb dystonia may be part of the clinical presentation of the syndrome.

3. Sepiapterin reductase deficiency, a rare but treatable paediatric movement disorder

Dopa responsive dystonias (DRDs) are a genetically heterogeneous subgroup of paediatric neurotransmitter diseases (PNDs), which occur due to defective tetrahydrobiopterin (BH4) metabolism. Since hyperphenylalaninemia, which is a useful marker in the screening of such diseases, is not always present, the disorders are classified based on the presence or absence of hyperphenylalaninemia. BH4 defects without hyperphenylalaninemia include dopa responsive dystonia (Segawa disease), sepiapterin reductase deficiency (SRD) and dihydrobiopterin reductase deficiency. BH4 defects without hyperphenylalaninemia include autosomal recessive GTP-1 cytohydroxylase deficiency, 6-pyruvoyl-teytrahydropterin synthase deficiency (6-PTS) and dihydropteridine reductase deficiency without hyperphenylalaninemia. In addition primary defects of monoamine synthesis include Tyrosine hydroxylase deficiency (TH) and Aromatic L-amino acid decarboxylase deficiency (AADC).

Examples of autosomal dominant and recessive types of dopa responsive dystonias are described. Segawa disease with autosomal dominant inheritance is a landmark in this group of diseases. Sepiapterin reductase deficiency (SRD) is a rare example of autosomal recessive variety [8]. It is caused by mutation in the SPR gene, located on the chromosome 2p14-p12 [9]. The clinical presentation includes cognitive delay along with dopa responsive mixed motor disorder often masquerading as cerebral palsy [10]. Neonatal screening tests are not helpful in the diagnosis of this disease since it is not associated with hyperphenylalaninemia. However the presence of certain additional clinical features like oculogyric crisis, diurnal fluctuation of the symptoms and hypersomnia provide a clue to the clinical suspicion. Clinical response to dopamine therapy is often rewarding and at times dramatic. The laboratory diagnosis of SRD is based on CSF analysis of neurotransmitter metabolites and pterins. The classical CSF findings in SRD include increased levels of sepiapterin along with reduced levels of 5-hydroxyindolacetic acid and homovanillic acid. The diagnosis can be confirmed by studying the SR activity in the fibroblasts and mutational analysis of the SPR gene.

The following paragraphs provide an overview of the clinical profile of SRD based on the information obtained from various case reports and recent reviews [11, 12] of Indian cases have been summarized.

3.1. Demography

Till date, a total number of 43 cases have been recognized from all over the world and are reviewed by Friedman et al. [11]. These include cases which are published and those documented in the international database maintained by the PND society. Both genders are equally represented. The cases belong to a wide ethnic background from various countries including India. A founder effect was suspected in the seven patients reported from Malta.

3.2. Clinical profile

3.2.1. Mixed motor signs and symptom

SRD causes symptoms related to dopamine and serotonin metabolism disturbances. The salient clinical features include motor and language delay associated with axial hypotonia, limb weakness, dystonia with diurnal fluctuation and oculogyric crisis. The latter group of symptoms often show sleep benefit. Other symptoms include parkinsonism, limb hypotonia, hypertonia and dysarthria. As against Segawa disease, the occurrence of dystonia is not universal in SRD. It is present in only about half of the cases. Less common neurological features include chorea, myoclonus and seizures.

The symptoms of SRD usually appear in age-related pattern [12]. The symptoms of axial hypotonia, tremors, hypersomnia, oculogyric crisis and sleep benefit usually appear in the first year of life while limb spasticity, diurnal fluctuation, dysarthria and dystonia become obvious between the ages of 2 and 6 years. The triad of oculogyric crisis, paroxysmal stiffening and axial hypotonia may be considered as a strong clue to suspect the diagnosis of SRD in the infantile group. However, these symptoms may persist or appear during late childhood as well. It is not unusual for the paroxysmal episodes to be misdiagnosed as seizure

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phenomenon resulting in delayed diagnosis and unwanted use of anticonvulsants. 'Cerebral palsy' is the commonest diagnosis in majority of the cases before reaching a final diagnosis.

3.2.2. Non-motor neurological features

These include sleep disturbances, behavioural changes and cognitive disabilities. Hypersomnia is the commonest sleep disturbance and present in nearly 50% cases especially in the infantile age group. Behavioural changes are also seen in slightly more than half of the cases. Cognitive disabilities of varying degree are seen in almost 90% cases. Nearly half of them have mental retardation, whereas others have mild-to-moderate disability.

3.2.3. Other features

Non-specific non-neurological features have been reported in SRD. These include pulmonary symptoms, vegetative symptoms such as gastrointestinal disturbances, hyperhidrosis, premature greying of hairs and menstrual abnormalities.

3.2.4. Salient investigations

CSF analysis is the mainstay of the diagnosis of SRD. The classical findings include

i) Low 5-hydroxyindolacetic acid and homovanillic acid levels.

ii) Elevated total biopterin, dihydrobiopterin and sepiapterin.

The study of SR activity in the fibroblast cultures has been performed in few cases and found to be confirmative. SR activity is either less or absent in such cases.

Genotyping of the documented 42 cases has revealed 16 mutations in the SPR gene. The intronic homozygous variant c596-2A>G is the most common genotype.

3.2.5. Treatment responses and outcomes

Substitution therapy is the mainstay of treatment in SRD. Most cases were treated either with L-dopa/carbidopa or benserazide (doses ranging from 1.45 mg to 20 mgm/kg/day) or 5-hydroxytryptophan (doses ranging from 0.65 to 5.9 mgm/kg/day). Combination therapy is also useful and in some cases better than the use of single drug. Other drugs used to treat include BH4, bromocriptine, anticholinergics, selegiline, sertraline and melatonin.

The response to treatment is always rewarding and at times dramatic. Patients may show improvement in motor activity and sleep disturbances within few hours of administering medication. Children who have been chair-bound or bed-bound may start moving and enjoy the unexpected relief with tremendous excitement. The rapid recovery is usually associated with appearance of choreiform dyskinesias requiring dose titration. Few cases show partial improvement. Favourable response to treatment is noted even in those cases who have received the treatment late in the course of their illness due to delayed diagnosis. Long-term follow-up has shown that few cases may require mild escalation in the dose of the drugs to maintain the favourable benefit. It also shows that response to therapy is not as complete as

seen in Segawa disease. Residual motor and cognitive dysfunction may persist. Early treatment is associated with better recovery.

3.2.6. Indian cases of SRD

Five Indian cases (three males and two females) of chemically and genetically proven SRD have been documented in the international database maintained by the PND society (BIODEF database IDs # 526,527,637,638 and 639) [13]. All of these cases have been reported from the Belgaum region of North Karnataka [11, 14]. These cases with consanguineous parenthood belonged to two independent families. The referring diagnosis in all these cases was 'cerebral palsy'. All cases showed very favourable and sustained response to L-dopa therapy (**Figure 3**). They have been followed up clinically for the past 5 years. The average maintenance dose of L-dopa was 1.5–2 mg/kg body weight in all these cases. All cases had the *core symptom complex* inclusive of psychomotor delay, axial hypotonia, limb hypotonia/hypertonia, acral dystonia/athetosis, diurnal variation and sleep benefit. **Table 1** summarises the clinical data which was present in addition to this core symptom complex.

Figure 3. This figure reveals the clinical state of the patient (BIODEF #523) of SRD before and after administration of levodopa. The left half of the figure shows evidence of truncal hypotonia and spastic-dystonia limb posturing. The right half of the figure shows the clinical state of the patient after administration of a single low dose of levodopa/carbidopa. The response was dramatic and seen within 12 hours.

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Case no. sex	Onset age	Age at diagnosis	Features additional to core symptom complex	Response to L-dopa/carbidopa therapy	5-year follow-up
1. Male	3 months	10 years	Premature greying of hairs/wheezing	Dramatic and well sustained to date	Independent, attends school and plays football
2. Female	3 months	11 months	Wheezing	Dramatic and well sustained to date	Independent, attends school and games
3. Male	9 months	5 years	Two episodes of seizures	Improvement noted after a week of initiating L-dopa therapy. Well-sustained to date	Independent. Attends school and regular games
4. Male	3 months	3 years	Irritable behaviour/ bilateral talipes equinovarus	Improvement noted after 1 week of initiating L-dopa therapy. Well-sustained to date	Independent and attends school. Scholastic performance is average
5. Female	3 months	1 year	Irritable behaviour with incessant crying/bilateral talipes equinovarus	Improvement noted after 1 week of initiating L-dopa therapy. Well-sustained to date	Stands and walks few steps independently. Does not attend school. Irritable behaviour

Table 1. Clinical summary of Indian cases of SRD.

It is likely that SRD is more common all over the world but possibly remains under-diagnosed due to lack of awareness and inadequate laboratory services. Such cases are likely to masquerade as 'cerebral palsy' and remain untreated for life.

4. Hereditary spastic paraplegia

Hereditary spastic paraplegia (HSP) is an untreatable rare genetic disorder, which causes long-term physical disability in the affected individuals. There is a high degree of genetic heterogeneity with over 60 causative genes identified so far. A collaborative study using whole genome sequencing (WSG) was performed in 10 HSP families from Belgaum in Karnataka, India. Pathogenic variants were identified in four consanguineous families. This included a novel frameshift homozygous deletion in *CYP2U1* (c.782_785delTCTG) gene in one family and a novel homozygous donor splice site variant in *DDHD2* (c.1125+1G>T) gene in another family. A probable genetic cause was identified in 40% of the families limited to consanguineous families in whom a family study was possible. Mutations were found in genes causing metabolic disorders such as Zellweger spectrum disorder and GM1 gangliosidosis. This study supports a role of WGS as a diagnostic tool in HSP [15].

4.1. Stem cell modelling of HSP

HSP is characterised by degeneration of long axons along the corticospinal tract, leading to lower limb spasticity. The mechanisms underlying HSP mutations that lead to degeneration of the long axons are unclear. Researchers have recently used patient-derived cells from the olfactory mucosa, a population of neural progenitor cells, derived from biopsies of the olfactory mucosa from HSP patients with SPAST mutations and from healthy controls, in order to identify cell functions altered in HSP [16]. Mutations in the SPAST gene account for the largest group of adult-onset HSP patients. These researchers show that SPAST patient-derived cells have reduced expression of protein Spastin (encoded by SPAST), reduced expression of stabilized microtubules, alterations in transport of cellular cargo and increased oxidative stress [17] (**Figure 4**). Based on their findings, Gautam Wali and colleagues propose that the downstream effects of SPAST mutations may cause a chronic state of oxidative stress in cortical motor neurons and other neurons, which ultimately leads to their degeneration, eventually manifesting the disease. They also show that the defects observed in the patient cells can be rescued using a microtubule-binding drug, Epothilone D. Epothilone D can cross the blood-brain barrier, making it a potential drug for HSP therapy [18].

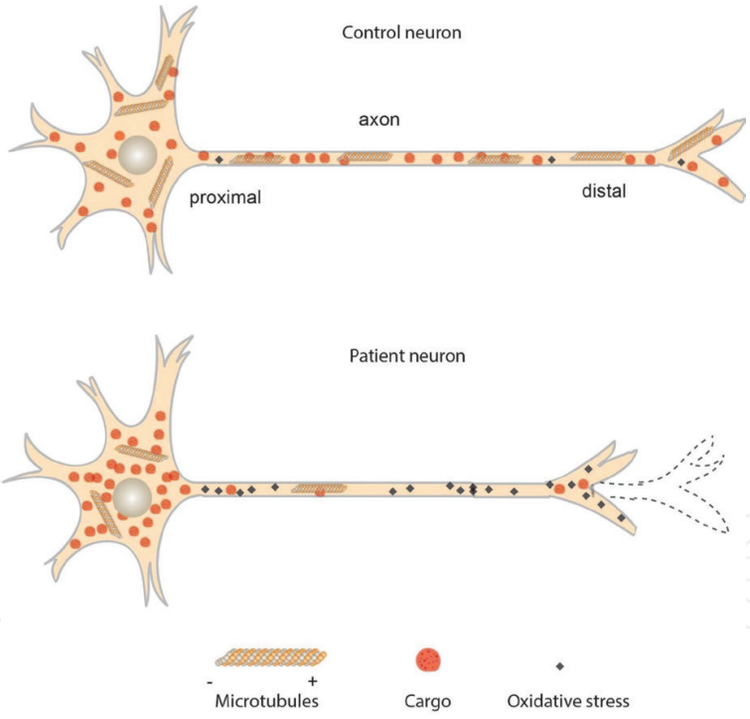

Figure 4. This figure summarises the mechanism of cell organelle dysfunction in HSP as confirmed by Gautam Wali and colleagues using patient-derived olfactory stem cells. They suggest a mechanism whereby *SPAST* mutations lead to reduced levels of stable microtubules which compromises cargo trafficking and leads to increased oxidative stress. These downstream effects of SPAST mutations may cause a chronic state of oxidative stress in cortical motor neurons and other neurons, which ultimately leads to their degeneration, eventually manifesting the disease. They also showed that Epothilone D, a microtubule-binding drug, can rescue the cell function defects in patient cells, making it a potential candidate for a future therapy for HSP.

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