Dystonias

Introduction

Dystonias are simultaneous contractions of opposing muscle pairs. They can be spasmodic or prolonged and may cause pain, posturing of affected body parts and contractures with severe disability. Sufferers experience a reduced quality of life and may have psychiatric illness. Some also experience stigmatisation.

There are various classifications for this movement disorder and a huge number of associated pathologies but currently, there is minimal understanding of disease pathophysiology. Many pharmacological and surgical treatment options are also available, most of which have been discovered through trial and error.

In this discussion, I shall delineate the pathophysiology of dystonias. I shall also outline a holistic approach to treating the condition, bearing in mind the complications of the disorder. I will also suggest future areas of research and methods of improving diagnostic efficiency.

Classification

Dystonias are classified on the basis of anatomical distribution, etiology and age of onset. Anatomically, they are further categorised into focal, segmental, multi-focal, unilateral and generalised dystonias. Focal dystonias involve a single body part i.e. the hand in writer’s cramp and the neck in torticollis (cervical dystonia). Segmental dystonias involve neighbouring regions of the body, for example, oromandibular dystonia or craniocervical dystonia. In the multifocal variant, affected body parts are well separated. Unilateral dystonia describes the situation where one half of the body is affected alone. Generalised dystonias affect large regions of the body and can be thought of as segmental dystonias with an additional, separate body part affected.1,2
Etiologically, the disorders are categorised according to whether they are of primary or secondary origin. Most primary dystonias have no genetic abnormalities associated with them. Others directly result from monogenic mutations. Dysfunctional proteins such as torsin-A and ε-sarcoglycan are associated with the primary dystonias. Transgenic mice models carrying these mutations however, do not develop the movement disorder. Instead, they display hyperactivity and impaired learning of motor skills. Thus the functional consequence of the mutations is not well understood.

The secondary dystonias may result from neurological and metabolic disorders such as Parkinson’s disease, Huntington’s disease, Wilson’s disease, Leigh’s disease and lipid storage diseases. Dystonias can also be unwanted effects of some medications i.e. dopamine antagonists and neuroleptics. Neo-natal hypoxic brain injury, hyperbilirubinaemia, cerebral infection and cerebral malformation can also result in secondary dystonias.

Age of onset is a further method of classification. Infantile dystonias start under the age of two whereas childhood dystonias begin between two to twelve years of age. Twenty years of age marks the boundary between juvenile and adult-onset dystonias.

The familiar dystonias
Torticollis usually begins in adulthood. It is characterised by spasmodic head movements starting between the ages of 30-50. It is the most common dystonia.

Occupational dystonias are also fairly common. These occur in people who perform repetitive hand movements as part of their vocation. Blepharospasm or eyelid twitches are also common. Dystonia musculorum deformans is a generalised dystonia causing
abnormal movements of the trunk and the limbs. It starts in childhood and adolescence. Lower limb, oromandibular and laryngeal dystonias are less common.

**Epidemiology**

The prevalence of dystonias is under-estimated. There are a number of reasons for this. Firstly, prevalence studies tend to focus on primary dystonias. They do not count focal variants secondary to neurological syndromes or separate focal dystonias as part of a generalised syndrome. This is illustrated by comparing the results of two prevalence studies. In one study, torticollis case numbers were obtained from neurologists at specialist treatment centres in eight European countries. From this, a prevalence of 57 per million was found. However, another study relying on individuals’ reports of a previous diagnosis of torticollis, found a much higher prevalence of 6900 per million. This second study utilised an online questionnaire that was distributed amongst the United States population.

It could be argued that the European study was not sensitive enough and was too specific. It only accounted for patients who were referred to tertiary treatment centres and these patients were diagnosed with torticollis alone. The second study was less specific but more sensitive as reports of torticollis were more often secondary to neurological diseases, medications or part of a segmental or multi-focal dystonia. It relied upon patients’ reports of previously being diagnosed. Clinicians treating the patients were however, not required to confirm diagnoses. This made the study less reliable.

Another factor contributing to the inaccurate prevalence figures is that 16-25% of affected patients have undiagnosed relatives with dystonia. Supporting this finding, the United States torticollis survey also found that 99% of patients with the disorder had at least one member of their household with head tilting and shaking.
The European study also noted a focal dystonia prevalence of 117 per million, a segmental dystonia prevalence of 32 per million and a multi-focal dystonia prevalence of 2.4 per million. A separate UK study found a prevalence of 14.2 per million for the primary generalised form. The prevalence of blepharospasm and writer’s cramp has been reported as 36 per million and 14 per million respectively. Oromandibular and laryngeal dystonia prevalences have been reported as 0.9 per million and 6.7 per million also.

**Factors affecting patient quality of life**

An SF-36 questionnaire distributed to 101 patients with torticollis found that sufferers had significantly lower scores for physical functioning, when compared with healthy subjects. They experienced poorer mental health, had less energy and vitality and experienced more pain compared with controls (p<0.05). Patients also showed a highly significant reduction in levels of energy, vitality and social functioning (p<0.001). Four weeks after botulinum toxin A injections at affected muscle sites, significant improvements in physical and social functioning, mental health, energy, vitality and pain occurred.

Depression and perceived stigma also contribute to a poorer health-related quality of life. Depression was found in 47.5% of patients in the previous study. In other studies, depression has been described in 47% of cases, social phobia is seen in 41.3%, panic disorder is noted in 29.5%, OCD (obsessive compulsive disorder) is noted in 6.8%-19.7% and substance misuse has been described in 13% of patients. Thus, there is a clear link between dystonia and psychiatric morbidity. Psychiatric comorbidity not only reduces patients’ ability to cope with any disability brought on by their disease, it can also increase the frequency and intensity of attacks. In fact, it has recently been shown that patients with comorbid depression show less...
improvement in health-related quality of life after therapeutic botulinum toxin injections. 9, 12, 13

Perceived stigma is also ignored. Patients with dystonia often describe feeling self-conscious and less attractive.14 This limits any benefits they may get from ‘opening up’ to confidants about their health problems. It may also lead to an avoidance of social contacts and isolation. Is this perceived stigma a reality, though? Do the general public hold negative opinions of dystonia sufferers? 80 biology students were shown videos of people with and without cranial and cervical dystonia. The students were told to score the people on the basis of likeability, attractiveness and trustworthiness amongst other things.14 Sufferers were judged to show significantly more negative qualities than the controls.14 However, the study only highlighted the opinions of young people (under-20 year olds) with similar backgrounds. Nevertheless, it did highlight that groups of people do hold consistently negative views of dystonia sufferers.

**Pathogenesis**

A number of cortical and extra-pyramidal cerebral abnormalities have been found in people with the condition. To recognise the effects of these abnormalities, one must first understand the normal integration of sensori-motor and basal ganglia activity in the brain.

During coordinated, purposeful body/limb movements, information about where the body or body parts are in space is utilised. The visual and primary somatosensory cortices provide this. The posterior parietal cortex integrates this information and from here it is forwarded to the prefrontal cortex, where a ‘plan’ is created for the body’s motor response. The prefrontal cortex sends electrical impulses to the SMA (supplementary motor area) and the PMA (premotor area). Here, the cortical circuitry
activates specific combinations of neurones in the primary motor cortex.\textsuperscript{15} The primary motor cortex then sends electrical signals to the muscles groups (via the spinal cord) required to carry out this unconsciously prepared movement. In order for fluid movement to occur, muscles that would oppose the movement are inhibited at this cortical level and at the spinal chord. This is called ‘reciprocal inhibition’.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{cerebral_cortex}
\caption{The passage of electrical impulses in the cerebral cortex, during coordinated body movements. The anatomical regions of the brain and the flow of information between them are shown. Adapted from\textsuperscript{15}.}
\end{figure}

Much information regarding the pathophysiology of dystonias has been gleaned from studying focal hand dystonias. Owl monkeys trained to perform repetitive hand activities showed disorganised sensory cortical mapping of that hand.\textsuperscript{16, 17} In humans, electrophysiological studies have shown that neurones representing particular digits of a hand, overlap with those on neighbouring digits.\textsuperscript{16} Maladaptive plasticity is also described in the sensory cortices of focal hand dystonia patients (through magnetic stimulation studies).\textsuperscript{18} It has thus been hypothesised that the deficient assimilation of sensory stimuli at the primary sensory cortex, combined with maladaptive plasticity, disrupts the sensory representation of the hand here. This process is exaggerated in occupational dystonias.
fMRI evidence of hypoactivity at the caudate and putamen of the basal ganglia also implicates impaired extra-pyramidal inhibition of cerebral motor outflow as contributing to dytonia pathogenesis. Other theories include aberrant reciprocal inhibition at the primary motor cortex (supported by transcortical magnetic stimulation studies).\textsuperscript{18, 19, 20}

Other types of dystonia have also been researched but their pathogeneses have not yet been elucidated. One reason for this is that in some cases, contradictory findings have emerged. For instance, in DYT1 and DYT5 (monogenic dystonias), reduced D\textsubscript{2} receptor binding and increased D\textsubscript{2} receptor binding at the putamen are respectively found.\textsuperscript{2}

Interestingly, one consistent observation has been noted through EMG (electromyographic) studies. Opposing muscles demonstrate a signature 4-7 Hz rhythmical electrical drive during dystonic contraction. This is consistent throughout the dystonias. Consequently, EMG can be implemented not just as a research tool, but as a diagnostic tool.\textsuperscript{21} This is significant when considering that it often takes a substantial amount of time to diagnose patients.\textsuperscript{5}

**Treatments**

The holistic treatment of dystonia involves a multi-faceted approach. Complications such as pain, contractures and disabling postures should be minimised. The frequency of dystonic attacks should be reduced, patients and the public should be educated about the condition and any psychiatric comorbidity should be treated.
Reducing dystonia complications

During simple attacks, steps on the analgesic ladder should be followed in order to relieve any pain and discomfort. Only during dystonic storm, (or status dystonicus) should one look to terminate attacks since the complications of such relentless continued attacks can be fatal. Hyper-pyrexia, rhabdomyolysis and renal failure are just some complications. All feasible means of terminating attacks should thus be considered (including anaesthetic options).22

Physiotherapy and muscle massage act to decrease the likelihood of contractures developing. Patients with generalised and segmental dystonias also benefit from back braces. These provide a sensory disturbance leading to fewer dystonic episodes. They also help patients to maintain functional postures.23

This unusual capacity to alleviate or even terminate dystonia attacks via sensory stimulation has been described in many dystonias. In blepharospasm, pressure on a specific sensory trigger point on the chin can do this1,2 as can transcutaneous vibratory stimuli applied to affected muscles in torticollis.23,24 Constraint-induced movement therapy also helps in focal hand dystonia.23,24 Here, some of the patient’s fingers are immobilised and he/she is instructed to move only the ambulatory digits. The hypothesised goal of these treatments is to reset the topography of the primary sensory cortex.

Reducing the frequency of dystonic events

BONT-A toxin injections at affected muscle sites are now the treatment of choice for focal and segmental dystonias. BONT-A inhibits SNAP-25, a component of the synaptosome complex responsible for releasing synaptic vesicle contents into the synaptic cleft. Thus, at the neuromuscular junction, it prevents the release of acetylcholine and paralyses culprit muscles.
A number of pharmacological options are also available. Tetrabenazine, an oral VMAT-2 (vesicular monoamine transporter – 2) inhibitor prevents the release of monoamines such as dopamine into synaptic clefts. Baclofen, a GABA\textsubscript{B} (gamma amino butyric acid) receptor agonist is used for treating generalised and spastic variants. Trihexyphenidyl, a centrally acting anti-cholinergic also shows some efficacy in treating dystonias. The benzodiazepines i.e. lorazepam and diazepam should be used for refractory cases. The dopa-responsive form is treated with L-dopa and carbamazepine.

The surgical options include unilateral and bilateral Gpi (globus pallidus internus) electrical stimulation or ablation. Bilateral subthalamic stimulation is an alternative. These are used most often in patients with generalised and multi-focal dystonias. Gpi stimulation is highly efficacious and is the surgical option most favoured. In a study involving 22 patients with primary generalised dystonia, 14 patients showed a >50% improvement in a movement disorder score, the BFMS (Burke-Fahn-Marsden scale), 12 months after bilateral Gpi stimulation therapy.

This surgery should only be considered in cases where all other treatment options have been tested. This is simply because of the current lack of understanding of the consequences of tampering with such delicate intra-cerebral structures. This minimal understanding, combined with reports of patients committing suicide post-surgically, has made people weary of administering such treatment. Consequently, further research on the neuropsychiatric complications of this type of surgery may be worthwhile.
Patient and public education

Bearing in mind that dystonia sufferers experience stigmatisation, the public should be educated about the condition. In lay terms, it should be communicated that dystonias have no behavioural or mental disability associated with them and that people who suffer from these disorders can for the most part, function like anybody else in society.

Patient education is also integral. Improving patient’s understanding of their condition may improve their compliance with treatment. Genetic counselling is also necessary for patients with generalised dystonia due to genetic mutations.

Treating psychiatric co morbidity

Psychiatric comorbidity is a problem for a substantial proportion of sufferers. This should not be ignored. The treatment approaches are not different from those used to treat psychiatric illness in the general population. There is one notable issue however. SSRIs (selective serotonin reuptake inhibitors) are implemented as first line when treating many psychiatric conditions. They occasionally precipitate dystonias themselves, though.\(^8\) TCAs (tricylic anti-depressants) and MAO-Is (monoamine oxidase inhibitors) can do the same but are less likely to do so.\(^8\) One should thus be cautious when prescribing anti-depressant here.

Future aims

A number of clinical wants have been alluded to in this paper. These include the need for further research and more rapid diagnosis and treatment of the condition. I shall discuss these further.

Many research questions still remain unanswered regarding the pathophysiology of the condition. Questions such as, why is it that some people develop occupational
dystonias, whereas others in the same line of work do not? Is it because some are inherently predisposed to cortical maladaptive plasticity and thus disorganisation of receptive fields after repetitive limb movements?

The literature on dystonia pathophysiology is bombarded with imaging evidence detailing the pathology observed in the different variants (particularly focal hand dystonia). However, there is little description of how this pathology has arisen. Seemingly, no one has researched the aberrant molecular biology that leads to maladaptive plasticity and disorganisation of receptive fields in dystonia. In recent years, glutamate-induced neurotrophin production has been implicated in synaptogenesis, neuronal axon and dendrite growth as well as cortical plasticity. Glutamate (a neurotransmitter) interacts with a number of post-synaptic receptors including NMDA (N-methyl-D-aspartic acid) and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate) receptors. This triggers calcium influx through the post-synaptic membrane. Calcium influx activates several transcription factors and thus the production of neurotrophins such as BDNF (brain-derived neurotrophic factor), NGF (nerve growth factor) and bFGF (basic fibroblast growth factor). BDNF is important for strengthening synaptic connections as well as promoting neurogenesis. It also plays an important role in cortical neuronal organisation and plasticity. Its aberrant actions here though, may lead to the pathology of focal hand dystonia and other dystonia variants.

Mapping neurotrophin distribution at the sensorimotor cortex, would allow one to identify sites of enhanced plasticity and receptive field disorganisation. This would enable targeted tissue sampling and in depth molecular biological research in experimental models. The pathophysiological processes that lead to dystonia could thus be further investigated.
I also feel that more research on mammalian models of non-focal hand variants is required to answer the many questions that still remain regarding the role that specific pathologies play in the development of dystonia. For example, is reduced D₂ receptor binding at the putamen a cause or consequence of the disease process?

There is still no complete explanation for the high rates of psychiatric illness in dystonia patients. Could the extra-pyramidal, cerebral or neurochemical pathologies explain this? OCD is characterised by abnormalities of the basal ganglia that are also seen in dystonia. Interestingly, BDNF levels are known to be reduced in the cerebral cortices of patients with depression. Further research is warranted here as patients’ quality of life can be dramatically improved if psychiatric morbidity is addressed.

Certainly the perceived stigmatisation and the pain and disability experienced by sufferers does not help lift patients’ mood. Patient stigmatisation must be addressed through public education campaigns and treatment must focus on minimising complications as well as relieving attacks. The diagnosis and treatment of dystonia must also be accelerated to prevent its complications becoming engrained. Diagnostic EMG technology should therefore be utilised.

**Summary**

Dystonias are complex disorders with variable classifications, pathogeneses and estimates of prevalence. Dystonia complications are also diverse and can dramatically reduce patients’ quality of life. I recommend that there needs to be further research into the disease pathophysiology, an enhanced public awareness and a more efficient means of diagnosis and treatment.
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