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Walking in the footsteps of James Parkinson 200 years on

Joan: 'So George let's test you, Grandad has been diagnosed with a condition recently, do you think you could diagnose him?'

George: 'Probably not, but I'll have a go, what was wrong grandad?'

Rod: 'It started with a tremor in my right hand that became annoying when I was sitting down, I just wanted to go get it checked out'

George: 'Ok anything else?'

Rod: 'I'm just a bit stiff all over really, can't really move as I used to. My handwriting has gone to pot too.'

Joan: 'So?'

George: 'Urm, Parkinson's?'

Joan & Rod gasp

Joan: 'How did you know that?'

George: 'I dunno, I guess it just came to me'

George (Thinking to himself): 'Actually I'd been lucky, we'd discussed it at school earlier that week.'

From then on, studying Parkinson's disease has been a passion of mine, with every piece of university coursework, including my dissertation revolving around this mysterious disease. Relating this to real life where I have seen my grandad deteriorate, with intermittent periods of relief and distress in equal number, the continuing struggle my grandmother has as his carer and the impact it has on the family has also given me a personal insight into the personal side to this awful condition. I have had many conversations with my Grandfather during this time regarding his disease which, to the best of my recollection, are accurate.

2017 holds the 200 year anniversary since James Parkinson published 'Essay on the Shaking Palsy'(1) containing stories and observations of 6 patients who he had stumbled across in the street. These 6 cases are scant of clinical details, however using these subjects he was able to differentiate between their shaking palsy from other causes of tremor, including that the shaking palsy is a mixture of tremor, slowness and gait disturbance as well as some non-motor features. He captured the clinical picture as thus:

'Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured'

At the time, this essay had very little impact until the mid-nineteenth century where Jean-Martin Charcot, a French neurologist, added rigidity to the signs identified by Parkinson and coined the term 'Parkinson's disease'.

Parkinson's description of the shaking palsy has now been updated in the BMJ where it is described as:

'Chronic progressive neurological disorder characterised by motor symptoms of resting tremor, rigidity, bradykinesia and postural instability. Insidious, often asymmetrical onset, associated with numerous, often disabling non-motor symptoms.'(2) This shows that James had a decent grasp on the condition; however there may be some differences which I believe we can forgive him for.

George: 'Grandad I've started doing a project on Parkinson's disease because of you'

Rod: 'Very good, what sort of things have you found?'

George: 'Well I've been looking at a particular protein that makes the body attack itself more which is thought to cause more severe PD. It's called LRRK2 and may be able to be targeted in treatments in the future'

Rod: 'Oh right, you've lost me'

George: 'Well let's just say it may hold the key to what's LRRK-ing around the corner'

Silence

Parkinson's disease has undergone lots of research since it was first described by James Parkinson, this ranges from what causes it, how it may be slowed, how symptoms are cured and how it may be stopped in it's track.

One of Charcot's most important contributions towards PD, apart from naming it was how he developed a way to classify tremorous disorders so that they could be differentiated. This was especially important between PD and multiple sclerosis. In the Sapletriere Hospital in Paris, he had a vast number of patients and therefore tremors that he could examine. He began to observe tremors in patient's both at rest and during active movements. He recognised that those with a rest tremor, such as in Parkinson's also presented with rigidity, slowed movements, a hunched posture and soft speech. This was in contrast to those with a tremor during action that had different features, including spasticity and weakness(3).

It was in 1925 that one of Charcot's pupils, Edouard Brissaud, first proposed that substantia nigra (SN) damage was to blame anatomically for Parkinson's Disease. This was further pursued by studies of the midbrain in the 1920s, which all agreed that the SN was indeed involved in the progression of PD(4).

Fast-forward to the 1960s when chemical differences in the brains of PD patients were identified. It was at this point that substantia nigra degeneration led to low levels of dopamine which was believed to cause the condition and therefore led to particular treatment patterns.

Currently several studies are being undertaken as to try and work out any biochemical mechanisms that lie behind PD and its causes. One of the potential causes is an enzyme called Leucine-rich repeat kinase 2 (LRRK2) that is encoded by the PARK8 gene(5). It has been found to have functions as a scaffolding protein, used to phosphorylate proteins and is also found in immunity cells. It is this function that is implicated to be at play in PD. When wild type LRRK2 is present in immune cells, it prevents an increase in Interleukins and therefore reduces the inflammatory process. However when mutated, LRRK2 can no longer prevent this increase, leading to more activated microglial cells, increasing neurodegeneration and therefore accelerating the presence of symptoms.

Rod: 'The important things are the treatments, what's the future going to be like for the people who get diagnosed in the future?'

George: 'There's plenty of research going on, you should hear what they used to use'

In 1817, James Parkinson devoted a chapter to 'considerations respecting the means of cure'. It was in this chapter where he discussed a treatment where 'the progress of the disease may be stopped'(1). This process of cure was by venesection of the neck until this area became blistered. Into these blisters, cork would be inserted to produce purulent discharge, allowing blood and inflammatory pressure to be diverted away from the nervous system, thus compressing the medulla, where Parkinson's believed neurological dysfunction stemmed from.

Charcot also had bizarre ideas on how to treat PD after noticing that after long rides in a horse and carriage, patients seemed to have lost some of the severity of their symptoms. Due to this observation, he invented a vibration therapy. He invited his patient to sit on a 'shaking chair' and began to shake them. This therapy then further progressed into a helmet which was deemed more appropriate as it was easier to transport. Fortunately these methods have now been long forgotten about in clinical practice.

He also adopted ideas of using anticholinergic drugs which improves the balance of cholinergic to dopamine neurotransmitters and seemed to improve Parkinsonian symptoms, however these are now only used in combination with first line treatment in those with persistent tremor.

The biggest breakthrough in treatment occurred when it was discovered that a deficiency in dopamine was the main cause of the disease and so dopamine replacement therapy has been the mainstay and gold standard in medication. This has further been developed so that other mechanisms can be used to increase the availability of dopamine in the SN and therefore increase symptom relief as seen in Cathecol-O-methyltransferase inhibitors and dopamine agonists including Ropinirole(6). However these drugs are used in symptom treatment and not curing the disease so maybe the future will bring more hope.

Further research is progressing into surgical treatments for PD which once again are used to alleviate symptoms. The most promising of these is deep brain stimulation where electrodes are implanted in the brain, generating pulses that reduce symptoms without some of the drug side effects.

Some standard medical techniques are also being turned into treatments such as the use of high strength ultra sound waves which can be used to cause lesions in the brain.

reducing tremors in some tremor based conditions and there is hope that this can be transferred to PD patients. This therefore reduces the risks of surgery and is a promising tool where relief can be provided during a single day with no overnight stay.

Conclusion

So 200 years since James Parkinson first described the disease has been an interesting mix of novel ideas, strange treatments and monumental breakthroughs. I think looking at what has occurred in this time, he'd be both elated yet also frustrated. He would see that many different techniques for controlling symptoms have been successful but he would be frustrated that there has only been one mainstay of treatment since the 1960s. However there would be hope, coming from new techniques that are currently in the early stages of development. More important to him, he'd be glad that his name will never be forgotten in the history of medicine.

References

1. Parkinson J. An essay on the shaking palsy. 1817. J Neuropsychiatry Clin Neurosci [Internet]. 2002 Jan;14(2):223–36; discussion 222.
2. Journal BM. BMJ Best Practice: Parkinson's Disease [Internet]. 2017 [cited 2017 Feb 17]. Available from: http://bestpractice.bmj.com/best-practice/monograph/147.html
3. Goetz CG. The Hitory of Parkinson's Disease: Early Clinical Descriptions and Neurological Therapies. Cold Spring Harb Perspect Med. 2011;1(1):1–16.
4. Parent M, Parent A. Substantia nigra and Parkinson's disease: a brief history of their long and intimate relationship. Can J Neurol Sci. England; 2010 May;37(3):313–9.
5. Greggio E, Civiero L, Bisaglia M, Bubacco L. Parkinson's disease and immune system: is the culprit LRRKing in the periphery? J Neuroinflammation [Internet]. ???; 2012 Jan [cited 2013 Jan 28];9(1):94.
6. Iversen SD, Iversen LL. Dopamine: 50 years in perspective. Trends Neurosci [Internet]. Elsevier; 2017 Feb 26;30(5):188–93.