

Wilson's Disease - A Rehabilitation Perspective

Introduction

Wilson's disease (WD) is a rare autosomal recessive inborn error of metabolism due to a defective WD gene, ATP7B, located on Chromosome 13q,¹ which causes low levels of the copper binding protein, caeruloplasmin. Spontaneous mutations are common. Copper accumulates in the liver, cornea and basal ganglia due to loss of the binding protein, reduced hepatic transport and reduced biliary secretion of copper.

Untreated Wilson's disease (hepatolenticular degeneration) is a relentlessly progressive and ultimately fatal disorder. A timely diagnosis and co-operation with life-long specific treatment removes the copper, prevents re-accumulation and prevents or treats the liver and brain damage.

Wilson's disease is not usually presented from a rehabilitation perspective. This account describes the clinical journey of a 23-year-old man with WD, who deteriorated catastrophically after initial penicillamine therapy. He needed intensive long-term neurorehabilitation for severe neurological and cognitive impairment that for some time looked irreversible. Although there are excellent reviews of the initial medical treatment of Wilson's,^{2,3} there is little available on rehabilitation outcomes⁴⁻⁷ and even less on evidence-based practice.

Case history

Presentation and treatment

This man presented with a six-month history of mild dysarthria, an asymmetric 'tapping' tremor at rest in his right hand, incoordination on walking and running, minor personality changes and uncharacteristic underperformance in his preceding year at University.

He moved stiffly, spoke softly and had variable rigidity of the right upper limb with dystonic hyperextension of the right thumb and tremor. Kayser-Fleischer (KF) corneal rings were seen and confirmed on slit lamp examination. His serum caeruloplasmin was very low at 4mg/dl (normal >20); serum copper was low, 5mmol/L (normal 11-24) and 24hr urinary copper excretion (with precautions to avoid contamination) was high with an average of 16.6mmol/24hr (normal<0.9). MRI brain scans showed typical abnormalities. His full blood count, renal parameters, and liver function tests were normal.

His parents were unrelated and there was no relevant family history. A diagnosis of Wilson's disease was confirmed. UK experts were consulted and involved in due course. Genetic testing found he was a compound heterozygote for two mutations of the Wilson gene, 524_525delAA and H1069Q and his siblings were then also screened. He was prescribed penicillamine, and started a low copper diet.

Deterioration

Within a week he developed a widespread erythematous rash, a moderate fever and loss of appetite, a sensitivity reaction which occurs in approximately 20% of individuals and usually resolves. His neurological condition then deteriorated quickly and dramatically. This is a known complication.⁸ He was bed-bound, his penicillamine was discontinued and he was readmitted as an emergency.

His voice was low volume and dysarthric with perseveration. Information processing, attentional skills, concentration and memory were all impaired contributing to reduced executive function. Eye movements and tracking were slowed and jerky. He had

severe cervical dystonia, his swallowing was impaired and he needed nasogastric feeding. He had marked rigidity in all four limbs with extreme dystonic flexion in his neck, right hand and right foot, severe resting tremor in his right thumb and hand, and mild left sided tremor. He was unconcerned with transient urinary and faecal incontinence. He was 'moody', uncooperative with therapy interventions and suspicious of hospitals and doctors.

Further management

Trientine, an alternative chelating agent was started, and benzhexol was continued. UK experts were consulted repeatedly over his management. He was severely disabled, was referred urgently for neurorehabilitation, and began intensive treatment 19 days after the onset of his reaction to the penicillamine.

Neurorehabilitation

He had inpatient neuro-rehabilitation for over twelve months with goal setting, regular case conferences and involvement of his family. Initially there was no significant change in his severe disability. Reference to a few case reports on the potential for late neurological and cognitive recovery encouraged the team and family that an intensive rehabilitation programme was worth pursuing.⁹⁻¹¹

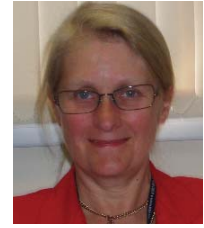
Verbal output was whispered, dysarthric and perseverative. He had severe antecollis with drooling and unsafe swallowing. Botulinum toxin injections into neck muscles improved head positioning from a marked tilt to the right to a lesser tilt to the left. The complexities of dealing with this dystonic, akinetic rigid state with cognitive impairment were becoming apparent.

Strategies to deal with mood swings, disinhibition and mildly sexualised behaviour were introduced by the psychologist and were partially successful. He remained distractible with poor concentration and attention skills for many months. Insight was slow to improve, as was his speed of information processing which came up from <1st percentile two months after diagnosis to the 16th percentile some eight months later.

Zinc acetate was introduced, after careful consideration and wide consultation, some seven months after his diagnosis was made, to try and speed up an intractably slow rate of change in his condition. This appeared to be associated with a faster rate of recovery. Zinc induces enterocyte metallothionein, promoting enteral binding of copper and slowly increases faecal copper excretion.¹² Careful dosing schedules avoiding interaction between trientine and zinc are necessary for maximal effect. He tolerated this combination well, although compliance was to become a significant issue.

His dominant right thumb was painfully dislocated at the MCP joint and was severely dystonic. After much discussion it was wired and splinted after a trial of Botulinum toxin. Botulinum toxin injections were also used repeatedly to reduce dystonia in the short and long flexors of his right foot, neck muscles, and forearm and hand muscles, with overall success. Throughout, he had serial splinting to his contractures, intensive physiotherapy and bespoke orthoses. The early goals were to maintain, or regain, muscle length and passive range of movement at all joints. A powered wheelchair helped his mobility and mood, and reduced his social isolation.

His initial Barthel ADL (Activities of Daily Living) Index score was 1/20 (totally dependent) and had only improved to 6/20 after three months of intensive reha-



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bilitation (continent, could shave with set-up, could feed using his left hand, and was no longer being hoisted for transfers) At six months his Barthel Index had improved to 11/20. He was using a power wheelchair, assisting with dressing, and transferring using a Rotunda turning frame. Distractibility and low mood were still preventing full cooperation. He began to practise walking first with a pulpit frame, then with two physiotherapists supporting and guiding him in the gym and in hydrotherapy. Progress remained slow due to dystonic contractures worse on the right side.

Improving range of movement was hindered by pain. The use of entonox (equal parts of nitrous oxide and oxygen) allowed examination and treatment under analgesia, demonstrating that movement was possible in an apparently dystonic, rigid and severely contracted limb. Although mutual trust had been re-established, changes in medication were still viewed with suspicion.

At twelve months he was walking independently with a wide based gait, upper body stiffness, head turned to the left, with contractures of right arm and leg, and postural tremor in the right leg. His toes were clawed. Botulinum injections to the long and short flexors of the right foot allowed him to get his foot flat on the floor for the first time. Left sided movements were now well coordinated with good hand function. The right hand was not functional. His Barthel had improved to 18/20. He needed help dressing his dystonic right foot, and could not cut up food. He had much greater insight into his cognitive impairments, was beginning to use strategies for poor memory, and could discuss his illness sensibly. He was encouraged to monitor his own progress, plan his own day and follow an exercise programme.

When his University were made aware of his illness they reconsidered his University record and decided to award him his degree. He became our first inpatient to obtain a degree while in hospital. Despite his progress it was clear that, at the end of inpatient rehabilitation, he had many unmet needs as well as potential for further improvement. He was not convinced and initially rejected our efforts to secure long term funding for further residential rehabilitation to work on vocational needs and independent living.

Outcomes

At the end of a year, he was discharged home to live with family. Compliance with medication, while sometimes erratic, was reasonable. Local outpatient therapy services were inadequate. This distressed him, his family and his inpatient team. Paradoxically, it helped secure funding and his cooperation to move on to a vocational placement.

After one year in a specialist residential rehabilitation centre he was keen to stay on for a second, reflecting significant improvement in cognitive skills and insight. He left in April 2007 and now lives independently using practised strategies to manage his time, monitor his mood and deal with periods of frustra-

tion and aggression.

Physically, he can run, swim and play some sport. He has been left with an abnormal posture of his dominant right hand. This is monitored; repeated treatments with Botulinum toxin and stabilising hand surgery have given him a functional improvement in grip and flexion control.

Cognitively there has been substantial recovery of his general IQ, memory skills, sustained and divided attention. He is still slow at processing new information. He is able to monitor speed and volume of speech, and communicates competently most of the time. Impulsive behaviour, distractibility and anger still occur but he manages them more effectively. He is now looking at supported employment options through ‘Ways into Work’.

Discussion points

1. Recovery is slow and protracted

Wilson’s disease is rare, affecting 1:30,000 of the population worldwide.¹ Few neurorehabilitation teams have experience in its management. At the start of this man’s rehabilitation journey his future looked bleak. An unwritten goal was to secure his full cooperation, that of his family and the treating team. The evidence as there was, suggested that a good outcome could be achieved. Four years after becoming symptomatic he is still improving.

2. Do no harm

Another unwritten goal was to do no harm – good clinical practice. The ease with which one dystonic deformity could be converted into another with Botulinum toxin, introduced a high degree of caution into our practice. Early hand surgery to correct deformities without addressing function, e.g. cosmetic tenotomies, could have been destructive. Frequent inter-specialty discussions maximised his prospects for a better recovery of muscular control.

3. Early treatment is not simple – consult the experts

Initial treatment of Wilson’s disease presenting with neuro-psychiatric symptoms is controversial.¹³⁻¹⁵ Penicillamine has been the mainstay of treatment but there is a risk of early neurological worsening, possibly due to rapid mobilisation of copper from the liver and its redistribution to the brain. It may be transient but can be catastrophic. In penicillamine intolerance or as first line treatment, trientine alone or a combination of trientine and zinc is now used. Once the central nervous system has been ‘de-coppered’, either trientine or zinc is continued long term. Lifetime surveillance and success of treatment is judged by serial 24hr urinary copper, serum copper levels and, in most instances, by the disappearance of KF rings. At all stages the management of this young man followed best advice and available evidence. Dimercaprol treatment was suggested shortly before his discharge from neurorehabilitation. Being able to cross the blood-brain barrier, it could

remove copper directly from the brain and perhaps stimulate further cognitive recovery. He considered the side effects of dimercaprol carefully and decided against it, with family support.

4. The patient and family are central to the large team of experts required for optimal recovery

His family was pivotal in anchoring his recovery and was the base from which his needs were evaluated and met. The people involved in his recovery were a truly multidisciplinary team. They included neurologists, nationally respected Wilson disease experts, a multi-disciplinary neurorehabilitation team, a hand surgeon and his team and lastly, life skills and vocational experts.

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