

A PATIENT THAT CHANGED MY PRACTICE

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Cold comfort pharm

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In a difficult case when either the diagnosis remains elusive, or the treatment does not seem to work, sit down and carefully review all the records—a lesson from Wilson's disease. Practical issues to do with drug treatment may be just as important as its efficacy.

During my training I was once advised that when managing neurological patients it was always important to have a further suggestion for therapy up one's sleeve in the event that the first treatments were unsuccessful. Nowadays this would probably be frowned upon as we are directed to rely on evidence rather than pragmatism, but what should one do when a patient with a condition known to be treatable fails to respond to all known therapies and there is no evidence base? When this happened recently I also recalled being told by another mentor (I think the editor of this journal, although it may have slipped his memory) that when you reach a dead end, either in diagnosis or treatment, you should sit down and review the whole set of notes to be sure nothing has been overlooked. The case I shall describe underlines the wisdom of this advice.

THE PROBLEM

A woman aged 21 presented more than 15 years ago with dysphagia, dysarthria, dribbling and twitching of the arms and was unequivocally diagnosed with Wilson's disease on the basis of appropriate physical and

biochemical findings. Treatment with D-penicillamine was started but had to be withdrawn because of a severe allergic reaction requiring hospital admission. She was then treated with trientine. This was supplied from the hospital pharmacy via a shared care protocol with the general practitioner (GP) and there was a clear and sustained improvement with almost total resolution of her neurological symptoms and signs over a period of months. Over the next few years the patient had two children and asked for the medication to be provided in containers with childproof lids. These were duly supplied by the pharmacy and the patient indicated at regular clinic attendances that she had plenty of medication.

Nine years after diagnosis the dysarthria and dystonia of the arms recurred and the dose of trientine was increased to the maximum, but despite this there was further neurological deterioration. Repeat investigations were consistent with Wilson's disease and after seeking advice, which indicated that it is very unusual in Wilson's disease to deteriorate on full treatment, a course of the chelating agent British anti-Lewisite (BAL) was given with resolution of the neurological signs.

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Two years later the patient again deteriorated and specialist advice was that this was most likely due to poor compliance with medication, although this was strongly denied by the patient and her husband. A further course of BAL resulted in improvement, but over the next few years three further courses of BAL had to be given because of episodes of neurological deterioration. Urinary copper had been measured on six occasions over the years as an in-patient and all had shown significant excess copper excretion. The importance of taking the medication regularly was repeated at clinic visits and this understandably caused some irritation because the patient was adamant that she was taking the medication as recommended, and indeed had more than sufficient supplies of the drug. Despite the addition of zinc treatment and dietary advice the episodes of deterioration were happening with increasing frequency. Attempts to obtain an alternative treatment, tetrathiomolybdate, were unsuccessful.

After the last course of BAL in 2006 there was only partial improvement, with disabling residual symptoms. I was asked by the patient just what I was going to do now. So, not knowing what to answer, I later sat down and looked through the two volumes of notes.

THE SOLUTION WAS EMBEDDED IN THE RECORDS

Among the expected in-patient notes, letters and investigation results there was a data sheet on trientine from the time this treatment was started in 1991, and on the reverse side was a paragraph on pharmaceutical precautions which stated: "Store at 2–8°C in a refrigerator. Stability trials have shown that when stored in original containers trientine is stable for at least one week at 37°C. Shelf life at 4°C 3 years." At the next clinic the patient reported that excess quantities of trientine had been provided by the pharmacy for some years and that, although the current tablet container was kept in the fridge as recommended, there were far too many bottles to keep all the supplies in this way. The excess was stored in a Welsh dresser in a corridor—next to a radiator—and was often there for weeks before being used. Advice from the manufacturer in 2006 was that "Trientine

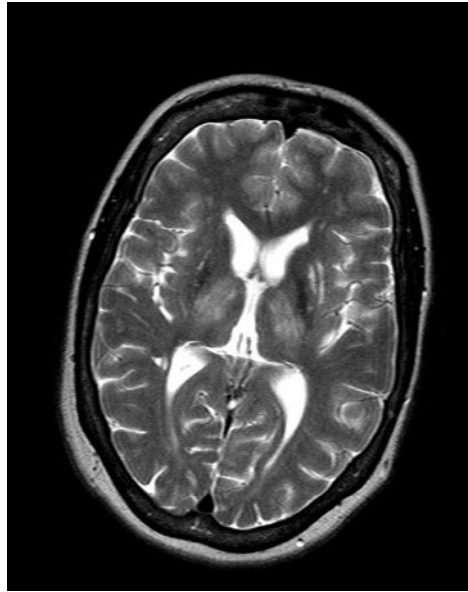


Figure 1
MRI brain scan of the case, showing changes typical of Wilson's disease.

should be stored at 2–8°C" and "Capsules should only be used if the temperature has not exceeded 25°C, the time out of controlled storage is less than 7 days and there is at least 12 months shelf life remaining". The pharmacist concluded that if this patient had kept the capsules out of the fridge for more than a week "the capsules will not be suitable for use and may be inactive!" and suggested that the current provision of 6 months supply at a time should be changed.

This seemed like a good, if somewhat belated, idea and since late 2006 the patient has been supplied more frequently with more manageable quantities of medication. The neurological symptoms and signs have since gradually improved and the patient now has virtually no residual problems and is better than she has been for years.

THE MESSAGE MAY APPLY TO OTHER CONDITIONS

This sequence of events indicates that the reason for the episodic deterioration in my patient's Wilson's disease was that the medication had been stored inappropriately in the home environment. This is an issue that may not often be considered by hospital specialists, or indeed GPs, and may be relevant to conditions other than Wilson's disease. When treatment unexpectedly fails, it may be worthwhile considering practical issues and not only information on efficacy.