

威爾遜氏症患者神經學的症狀是否可以經由藥物改善

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About the case

- ◆ A 41y/o male had the history of Wilson disease since 民國89 at KMUH.
- ◆ His clinical presentation was left side weakness, unsteady gait and dysarthria, and cognition function was well.
- ◆ Penicillamine and Zinc were used for his Wilson's disease. But allergic reaction to Penicillamine was found. We try to found alternative treatment for Wilson disease.

Back Ground

- ◆ Wilson disease is an autosomal recessive disease of a toxic reaction to copper, primarily affecting the brain and liver.
- ◆ 50% of patients presenting with neurologic symptoms treated with penicillamine had neurologic deterioration, and 77% of these were in the first weeks.

Back Ground

- ◆ Zinc therapy takes 4 to 6 months to control the toxic effects of copper.
- ◆ Trientine: Its effectiveness is less than that of penicillamine, but the incidence of toxicity and hypersensitivity reactions is lower.
- ◆ Tetrathiomolybdate (TM) forms a complex with protein and copper and blocks the absorption of copper. The major drawback to using this drug is that it still has not been approved for general use in this country.

Clinical Problem

- ◆ Patients Question:
 - Is there any new treatment available for symptom control?
- ◆ Ammonium Tetrathiomolybdate in the treatment of Wilson disease
- ◆ Comparison of its benefit and side effect with trientine

PICO

- ◆ P- Patients of Wilson disease presenting with neurologic symptoms
- ◆ I- Ammonium Tetrathiomolybdate
- ◆ C- Trientine
- ◆ O- Neurological outcome

Key words

- ◆ Ammonium Tetrathiomolybdate
- ◆ Trientine
- ◆ Wilson disease

搜尋步驟

◆ Cochrane Library ----1/1

- Treatment of Wilson disease with ammonium tetrathiomolybdate: IV. Comparison of tetrathiomolybdate and trientine in a double-blind study of treatment of the neurologic presentation of Wilson disease

Arch Neurol. 2006 Apr;63(4):521-7

搜尋步驟

◆ ACP journal club ---- 1/1

- Treatment of Wilson disease with ammonium tetrathiomolybdate: IV. Comparison of tetrathiomolybdate and trientine in a double-blind study of treatment of the neurologic presentation of Wilson disease

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搜尋步驟

◆ Pubmed ---- 2/29

- Treatment of Wilson Disease With Ammonium Tetrathiomolybdate III. Initial Therapy in a Total of 55 Neurologically Affected Patients and Follow-up With Zinc Therapy

Arch Neurol. 2003;60:379-385

- Treatment of Wilson disease with ammonium tetrathiomolybdate: IV. Comparison of tetrathiomolybdate and trientine in a double-blind study of treatment of the neurologic presentation of Wilson disease

Arch Neurol. 2006 Apr;63(4):521-7

結果摘要-1

- ◆ Treatment of Wilson disease with ammonium tetrathiomolybdate: IV. Comparison of tetrathiomolybdate and trientine in a double-blind study of treatment of the neurologic presentation of Wilson disease
- ◆ Objection: To compare tetrathiomolybdate and trientine in treating patients with the neurologic presentation of Wilson disease for the frequency of neurologic worsening, adverse effects, and degree of neurologic recovery.

結果摘要-1

- ◆ Tetrathiomolybdate (TM):
 - Given with food, TM binds food copper and endogenously secreted copper with food proteins and prevents absorption of the complexed copper.
 - Given without food, TM is absorbed into the blood and there complexes available copper with albumin, making the copper unavailable for cellular uptake.

結果摘要-1

- ◆ **Method:**
- ◆ Randomized, double-blind, controlled, 48 patients with the neurologic presentation of Wilson disease.
 - Trientine hydrochloride 500 mg BID for 8 weeks
 - Tetrathiomolybdate 20 mg 3 times per day with meals and 20 mg 3 times per day between meals for 8 weeks.
- ◆ All patients received 50 mg of zinc BID
- ◆ Most patients → newly diagnosed
- ◆ ITT design

結果摘要-1

- ◆ Hospitalization for 8 weeks, discharged taking 50 mg of zinc TID, and returned annually for follow-up.
- ◆ Neurologic and speech function assessed weekly
 - Neurologic examination (scale, 0-38) (5 points)
 - Speech examination (scale, 0-7) (3 points)
- ◆ Anemia, Leukopenia, Transaminase elevations (either ALT or AST)

結果摘要-1

- ◆ **Results and comments:**
- ◆ Neurologic deterioration in 6 of 23 (26%) patients in the trientine arm compared with 1 of the 25 (4%) patients in the TM arm → statistically significant ($P < 0.05$).
- ◆ Long-term neurologic recovery overall was very good
- ◆ Speech recovery was fair and did not differ between the 2 arms.

結果摘要-1

Table 2. Patients' Neurologic Scores

	Baseline	Week								
		1	2	3	4	5	6	7	8	38
24 Patients in the TM Arm Who Did Not Show Neurologic Deterioration										
Mean (SD)	7.7 (5.1)	7.4 (5.3)	7.7 (5.7)	7.5 (5.5)	7.6 (5.7)	8 (5.3)	7.2 (5.2)	5.8 (3.8)	5.1 (3.2)	
Sample size	24	16	17	21	21	21	17	14	12	
1 Patient in the TM Arm Who Showed Neurologic Deterioration										
Patient 251	7.5		7.5	9.5	13		11.5			
17 Patients in the Trientine Hydrochloride Arm Who Did Not Show Neurologic Deterioration										
Mean (SD)	8.9 (7.2)	8 (5)	8.6 (7.4)	8.5 (7.6)	9.1 (6.4)	8.1 (6.5)	8.2 (6.9)	10.0 (8.7)	9.3 (11.1)	
Sample size	17	11	12	12	15	15	15	7	5	
6 Patients in the Trientine Arm Who Showed Neurologic Deterioration										
Patient										
76	7.0	8.0	10.0	15.0	17.5	18.0	18.0	20.0		
233	10.5	12.0			18.5		19.5	20.5	22.5	
238	3.5		2.0	7.5	10.5	10.0		9.5		
243	15.0	15.0	14.0	14.0	14.0	14.5	20.5	17.0		
260	11.5	11.5	12.0	11.5	12.0	10.5	10.5		10.0	
287	11.0	9.8	10.8	14.8	15.0	14.8	15.0	17.3	17.3	17.5

結果摘要-1

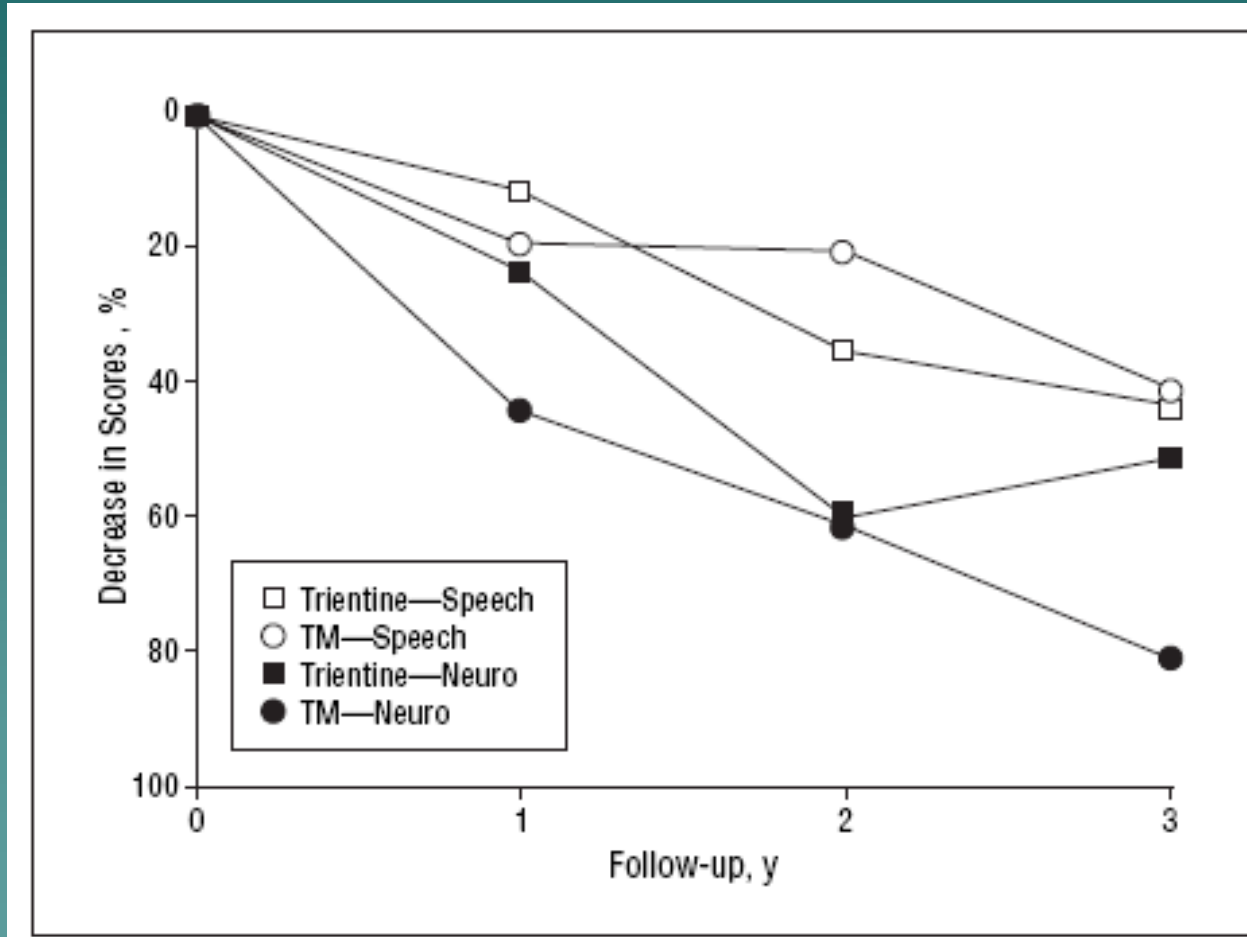
- ◆ Baseline speech scores of the patients who did not deteriorate neurologically averaged **3.32**.
- ◆ Baseline speech scores of the 7 deteriorated patients averaged **4.64**.
- ◆ This suggests that a high baseline speech score is predictive of neurologic deterioration during treatment.
- ◆ None of 25 patients with a baseline speech score of 3.5 or less deteriorated.
- ◆ 7 of 24 patients with baseline scores of 4.0 or higher deteriorated.

結果摘要-1

Table 3. Patients' Speech Scores

	Baseline	Week								
		1	2	3	4	5	6	7	8	38
24 Patients in the TM Arm Who Did Not Show Neurologic Deterioration										
Mean (SD)	3.1 (1.6)	3.3 (1.6)	3.3 (1.6)	3.3 (1.8)	3.0 (1.7)	3.2 (1.6)	2.8 (1.6)	3.3 (1.5)	3.0 (2.0)	
Sample size	24	18	20	16	20	22	14	16	15	
1 Patient in the TM Arm Who Showed Neurologic Deterioration										
Patient 251	5.0	5.0	5.0	5.5	6.0	6.0				
17 Patients in the Trientine Hydrochloride Arm Who Did Not Show Neurologic Deterioration										
Mean (SD)	3.6 (1.6)	3.6 (1.6)	3.5 (1.4)	3.9 (1.3)	3.7 (1.8)	3.8 (1.8)	3.6 (1.7)	3.3 (1.7)	3.6 (2.4)	
Sample size	17	15	13	15	13	12	15	13	4	
6 Patients in the Trientine Arm Who Showed Neurologic Deterioration										
Patient										
76	5.0	6.0	5.0	5.5	5.0			4.5	4.5	
233	4.5		5.0	6.0		5.5	5.5	5.5	5.5	
238	4.0	3.0	3.0	4.0	3.0	4.5		4.0		
243	5.0	5.0	4.5	4.5	4.5	5.5	5.5	6.0	4.5	
260	4.0	3.5	3.5	4.0	4.0	4.0	4.0		4.0	6.0
287	5.0	4.5	6.0	5.5		7.0	6.0	5.0		

結果摘要-1



結果摘要-1

- ◆ Trientine was well tolerated. Only 1 patient developed anemia/leukopenia.
- ◆ Tetrathiomolybdate showed a frequency of about 12% of anemia and/or leukopenia (3 of 25 patients) and about 16% of transaminase elevations (4 of 25 patients).
- ◆ 2 patients in the TM arm died during follow-up. One of these was the patient who had neurologic deterioration. However, he died of leukemia presumably unrelated to Wilson disease or its therapy.
- ◆ 4 patients in the trientine arm died during follow-up. 3 of these were patients who deteriorated neurologically while receiving trientine therapy.

結果摘要-1

Table 5. Deaths in the 48 Patients

Treatment Arm	Patient	Months Until Death	Cause of Death
Trientine hydrochloride	233	22	Severe neurologic impairment, general inanition, infection
	260	11.5	Neurologic deterioration beginning soon after hospital discharge, general inanition
	280	12	Severe neurologic impairment initially, no improvement, general inanition
	287	6	Severe neurologic impairment, pulmonary congestion
TM	249	14	Severe neurologic impairment initially, no improvement, late neurologic worsening, general inanition
	251	17.5	Leukemia

結果摘要-1

- ◆ This study suggests that neurologic deterioration during initial treatment with trientine is a **grave** prognostic sign.
- ◆ Of the other 17 patients who did not deteriorate, only 1 died.
- ◆ Of the 6 patients treated with trientine who deteriorated, 3 died. (1 worsen, 1 as baseline, 1 well)

結果摘要-1

- ◆ The 7- to 8-week value for urine copper reflects the effect of the drug on urinary copper excretion.
- ◆ Urine copper values at 1 year show that the urine copper has come under good control (while the normal value is $\leq 50 \mu\text{g}$, values lower than $125 \mu\text{g}$ are viewed as under good control).
- ◆ The normal value for nonceruloplasmin plasma copper is about $10 \mu\text{g/dL}$, so the values at 1 year show good control.

結果摘要-1

Table 6. 24-Hour Urine Copper and Nonceruloplasmin Plasma Copper Values*

	TM			Trientine Hydrochloride		
	Initial	7-8 wk	1 y	Initial	7-8 wk	1 y
24-h urine copper level, μg	240 (20)	213 (23)	89 (10)	270 (60)	1102 (50)	116 (30)
Nonceruloplasmin plasma copper level, $\mu\text{g/dL}$	17.2 (2.3)	11.8 (4.3)	7.4 (1.7)	10.7 (2.2)	11.8 (3.6)	7.3 (1.5)

結果摘要-1

- ◆ **Conclusion:**
- ◆ Neurologic deterioration higher in the trientine arm in the TM arm (statistically significant)
- ◆ Long-term neurologic recovery overall was very good
- ◆ Speech recovery was fair and did not differ between the 2 arms.
- ◆ High baseline speech score is predictive of neurologic deterioration during treatment.
- ◆ Trientine was well tolerated. TM had the high risk of anemia, leukopenia and liver function elevation
- ◆ Neurologic deterioration during initial treatment with trientine is a **grave** prognostic sign.

Level of Evidence

- ◆ Evidence level 2b
 - Only 20/48 patient left in the study after 8 weeks treatment and there was no further explanation and statistical data of withdrawers

結果摘要-2

- ◆ Treatment of Wilson Disease With Ammonium Tetrathiomolybdate III. Initial Therapy in a Total of 55 Neurologically Affected Patients and Follow-up With Zinc Therapy
- ◆ Background: It is unclear what anticopper drug to use for patients with Wilson disease who present with neurologic manifestations because **penicillamine often makes them neurologically worse and zinc is slow acting.**
- ◆ Objective: To evaluate the frequency of neurologic worsening and drug adverse effects with ammonium tetrathiomolybdate

結果摘要-2

- ◆ In many patients the drug was started at 120 mg/d, with 20 mg between meals 3 times daily and 20 mg with meals 3 times daily.
- ◆ In most patients the between-meals doses were then rapidly escalated during a several-day period, usually to a total dose of about 200 to 260 mg/d. In some patients, the dose was not escalated.
- ◆ Patients also started zinc therapy early in their 8-week stay, usually 50 mg 3 times per day.
- ◆ Patients did not receive additional tetrathiomolybdate after the initial 8 weeks of therapy.

結果摘要-2

- ◆ Quantitative neurologic test and speech examination weekly
 - Increase of 5 points (scale, 0-38) on the quantitative neurologic examination
 - Increase of 3 points (scale, 0-7) on the speech examination
- ◆ Blood cell counts, liver function tests, and amylase, lipase, creatinine, serum urea nitrogen, uric acid, urine protein, and iron variables
- ◆ Follow up for 3 years

結果摘要-2

- ◆ **Results and Comment**
- ◆ One of 22 patients showed a 6-point deterioration in week 2, so we scored her as showing deterioration, although her scores varied quite widely during the next 3 weeks.
- ◆ Only 1 patient showed significant deterioration, in this case between baseline and year 1, and this was clearly related to noncompliance with zinc therapy.
- ◆ No patient showed a 3-point deterioration (increase) in speech score, and show statistically significant improvement between baseline and year 1.

結果摘要-2

- ◆ Putting these data together with data from the earlier 33 patients described, of whom 1 deteriorated, we have seen a total of 2 neurologic deteriorations in 55 patients treated, for a rate of 3.6%.
- ◆ 5 of 22 patients exhibited bone marrow suppression → anemia or leukopenia
- ◆ The frequency of anemia or leukopenia was much higher in the current study (5/22) than in the earlier study (1/33).

結果摘要-2

- ◆ 3 of 22 patients exhibited elevations of serum aminotransferase enzymes
- ◆ Aminotransferase elevations in 3 of 22 patients, was not detected at all in the earlier study of 33 patients.
- ◆ One difference is that the number of patients receiving a daily dose of 200 mg or more was only 15 of 33 in the original study and was 14 of 22 in the present study.

結果摘要-2

- ◆ A second difference is that the dose escalation was considerably more rapid in the current study, usually taking less than a week, while it occurred during 2 to 3 weeks in the original study.
- ◆ The most important difference is that in the original study, escalation was based on the presence of free copper in the blood. In the current study, escalation was more arbitrary, aimed at quelling copper toxicity quickly.

Conclusion

- ◆ Penicillamine is not suitable for patient of Wilson disease with neurological symptoms.
- ◆ Zinc: the onset of effect is too slow
- ◆ Neurologic deterioration higher in the trientine arm in the TM arm (statistically significant) (Grade B)
- ◆ Trientine had the low risk of side effect, but had the higher death rate (Grade B)
- ◆ Ammonium Tetrathiomolybdate with Zinc is the suggestive treatment protocol for neurological deficit improving. (Grade B)

Application

- Are those evidence beneficial to our treatment plan?
 - NO, Tetrathiomolybdate is not currently available in our country.
 - Yes, we do have much better understanding of how trientine act to this patient and we know there is another alternate rather than trientine. Which would likely to be beneficial in case he's a non-responder to trientine.

Follow-up

- ◆ Patient had been watched in my clinic for more than 2 months, and he is a responder to Trientine. He speaks better now. Which is not a poor prognostic sign for long term neurological deficit.

◆ Thanks for your attention