

脊髄小脳変性症に対する真武湯，当帰芍薬散の有用性

- 経頭蓋磁気刺激法との併用において -

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抄 録

脊髄小脳変性症 (SCD) に対する真武湯と当帰芍薬散の効果を検討した。対象は SCD 患者 5 名。皮質小脳萎縮症 (CCA) 2 例，spinocerebellar ataxia type 1 (SCA1) 1 例，オリブ橋小脳萎縮症 1 例で，東洋医学的には (5 例) 全例が陰・虚証であった。倦怠感を伴った 1 例 (CCA) には当帰芍薬散を投与し，残りの 4 例には真武湯を投与した。投与前と投与後 3 カ月および経頭蓋磁気刺激法施行後にその効果を international cooperative ataxia rating scale (ICARS) にて評価した。

ICARS では投与前後で有意な変化はみられなかったが，全例でふらつき感が改善した。また，当帰芍薬散を投与した例では倦怠感も改善し，両方剤は SCD の自覚症状を改善させた。また真武湯を投与した 4 例では，経頭蓋磁気刺激法を併用したところ，ICARS の低下を認め，経頭蓋磁気刺激法との併用が有用であった。

索引用語

脊髄小脳変性症，真武湯，当帰芍薬散，経頭蓋磁気刺激法

緒 言

真武湯¹⁻⁴⁾ や黄耆建中湯⁵⁾ が脊髄小脳変性症に対して有用であったという報告がある。当科でも脊髄小脳変性症患者 4 例に真武湯を処方したところ，ふらつき感が改善した。また，当帰芍薬散を処方した症例では倦怠感も改善した。真武湯，黄耆建中湯，当帰芍薬散に共通している成分は芍薬である。芍薬は脊髄小脳変性症の自覚症状に対して有用である可能性があり，文献的考察を加え報告する。

対 象

脊髄小脳変性症 (spinocerebellar degeneration; SCD) 患者 5 名で，平均年齢 57.8 ± 17.9 歳，男性 2 例，女性 3 例。内訳は皮質小脳萎縮症 (cortical cerebellar atrophy; CCA) 2 例，spinocerebellar ataxia type 1 (SCA1) 1 例，オリブ橋小脳萎縮症 (olivopontocerebellar atrophy; OPCA) 2 例である。診察にて陰・虚証であることを確認した。具体的には，小脳性運動失調症のために体力を消耗しており「虚」，手足は自律神経障害のため冷たく「寒」，病巣は脳深部の小脳・脳幹・脊髄にあるために「裏」であり，総合的に「陰・虚」と判断した。

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Table 1 International Cooperative Ataxia Rating Scale (ICARS)⁹⁾.

| | | |
|--|---|---|
| <p>I. Posture and gait disturbances</p> <p>1. Walking capacities (Observed during a 10-meter test including a half-turn, near a wall, at about 1.5 meter.)</p> <p>0 = Normal 1 = Almost normal naturally, but unable to walk with feet in tandem position</p> <p>2 = Walking without support, but clearly abnormal and irregular 3 = Walking without support but with considerable staggering; difficulties in half turn 4 = Walking with autonomous support no longer possible; the patients uses the episodic support of the wall for a 10-meter test 5 = Walking only possible with one stick 6 = Walking only possible with two special sticks or with a stroller 7 = Walking only with accompanying person 8 = Walking impossible, even with accompanying person (wheelchair)</p> <p>Score: ...</p> <p>2. Gait speed (Observed in patients with preceding scores 1-3; preceding score 4 and up gives automatically score 4 in this test.)</p> <p>0 = Normal 1 = Slightly reduced 2 = Markedly reduced 3 = Extremely slow 4 = Walking with autonomous support no longer possible</p> <p>Score: ...</p> <p>3. Standing capacities, eyes open (The patient is asked first to try to stay on one foot, if impossible, to stand with feet in tandem position; if impossible, to stand feet together; for the natural position, the patient is asked to find a comfortable standing position.)</p> <p>0 = Normal: able to stand on one foot more than 10 s 1 = Able to stand with feet together, but no longer able to stand on one foot more than 10 s 2 = Able to stand with feet together, but no longer able to stand with feet in tandem position 3 = No longer able to stand with feet together, but able to stand in natural position without support, with no or moderate sway 4 = Standing in natural position without support, with considerable sway and considerable corrections 5 = Unable to stand in natural position without strong support of one arm 6 = Unable to stand at all, even with strong support of two arms</p> <p>Score: ...</p> <p>4. Spread of feet in natural position without support, eyes open (The patient is asked to find a comfortable position; then the distance between medial malleoli is measured.)</p> <p>0 = Normal (< 10 cm) 1 = Slightly enlarged (> 10 cm) 2 = Clearly enlarged (25 cm < spread < 35 cm) 3 = Severely enlarged (> 35 cm) 4 = Standing in natural position impossible</p> <p>Score: ...</p> <p>5. Body sway with feet together, eyes open</p> <p>0 = Normal 1 = Slight oscillations 2 = Moderate oscillations (< 10 cm at the level of head) 3 = Severe oscillations (> 10 cm at the level of head), threatening the upright position 4 = Immediate falling</p> <p>Score: ...</p> <p>6. Body sway with feet together, eyes closed</p> <p>0 = Normal 1 = Slight oscillations 2 = Moderate oscillations (< 10 cm at the level of head) 3 = Severe oscillations (> 10 cm at the level of head), threatening the upright position 4 = Immediate falling</p> <p>Score: ...</p> <p>7. Quality of sitting position (Thighs together, on a hard surface, arms folded.)</p> <p>0 = Normal 1 = With slight oscillations of the trunk 2 = With moderate oscillations of the trunk and legs 3 = With severe dysequilibrium 4 = Impossible</p> <p>Score: ...Posture and gait score (static score): .../34</p> | <p>II. Kinetic functions</p> <p>8. Knee-tibia test (decomposition of movement and intention tremor) (The test is performed in the supine position, but the head is tilted, so that visual control is possible. The patient is requested to raise one leg and place the heel on the knee, and then slide the heel down the anterior tibial surface of the resting leg towards the ankle. On reaching the ankle joint, the leg is again raised in the air to a height of approximately 40 cms and the action is repeated. At least 3 movements of each limb must be performed for proper assessment.)</p> <p>0 = Normal 1 = Lowering of heel in continuous axis, but the movement is decomposed in several phases, without real jerks, or abnormally slow 2 = Lowering jerkily in the axis 3 = Lowering jerkily with lateral movements 4 = Lowering jerkily with extremely strong lateral movements or test impossible</p> <p>Score right: ...Score left: ...</p> <p>9. Action tremor in the heel-to-knee test (Same test as preceding one: the action tremor of the heel on the knee is specifically observed when the patient holds the heel on the knee for a few seconds before sliding down the anterior tibial surface; visual control is required.)</p> <p>0 = No trouble 1 = Tremor stopping immediately when the heel reaches the knee 2 = Tremor stopping in less than 10 seconds after reaching the knee 3 = Tremor continuing for more than 10 seconds after reaching the knee 4 = Uninterrupted tremor or test impossible</p> <p>Score right: ...Score left: ...</p> <p>10. Finger-to-nose test: decomposition and dysmetria (The subject sits on a chair; the hand is resting on the knee before the beginning of the movement; visual control is required. Three movements of each limb must be performed for proper assessment.)</p> <p>0 = No trouble 1 = Oscillating movement without decomposition of the movement 2 = Segmented movement in 2 phases and/or moderate dysmetria in reaching nose 3 = Segmented movement in more than 2 phases and/or considerable dysmetria in reaching nose 4 = Dysmetria preventing the patient from reaching nose</p> <p>Score right: ...Score left: ...</p> <p>11. Finger-to-nose test: intention tremor of the finger (The studied tremor is that appearing during the ballistic phase of the movement; the patient is sitting comfortably, with his hand resting on his/her thigh; visual control is required; three movements of each limb must be performed for proper assessment.)</p> <p>0 = No trouble 1 = Simple swerve of the movement 2 = Moderate tremor with estimated amplitude < 10 cm 3 = Tremor with estimated amplitude between 10 cm and 40 cm 4 = Severe tremor with estimated amplitude > 40 cm</p> <p>Score right: ...Score left: ...</p> <p>12. Finger-finger test (action tremor and/or instability) (The sitting patient is asked to maintain medially his/her 2 index fingers pointing at each other for about 10 s, at a distance of about 1 cm, at the level of the thorax, under visual control.)</p> <p>0 = Normal 1 = Mild instability 2 = Moderate oscillations of finger with estimated amplitude < 10 cm 3 = Considerable oscillations of finger with estimated amplitude between 10 and 40 cm 4 = Jerky movements > 40 cm of amplitude</p> <p>Score right: ...Score left: ...</p> <p>13. Pronation-supination alternating movements (The subject, comfortably sitting on a chair, is asked to raise his/her forearm vertically and to make alternative movements of the hand. Each hand is moved and assessed separately.)</p> <p>0 = Normal 1 = Slightly irregular and slowed 2 = Clearly irregular, and slowed, but without sway of the elbow 3 = Extremely irregular and slowed movement, with sway of the elbow 4 = Movement completely disorganised or impossible</p> <p>Score right: ...Score left: ...</p> | <p>14. Drawing of the Archimedes' spiral on a pre-drawn pattern (The subject is comfortably settled in front of a table, the sheet of paper being fixed to avoid artefacts. The subject is asked to perform the task without timing requirements. The same conditions of examination must be used at each examination: same table, same pen. The dominant hand is examined. For assessment, see joined examples at the end of this section.)</p> <p>0 = Normal 1 = Impairment and decomposition, the line quitting the pattern slightly, but without hypermetric swerve 2 = Line completely out of the pattern with recrossings and/or hypermetric swerves 3 = Major disturbance due to hypermetria and decomposition 4 = Drawing completely disorganised or impossible</p> <p>Score: ...Kinetic score (limb coordination): .../52</p> <p>SCORING OF THE DISTURBANCES OF DRAWING IN THE ARCHIMEDES' SPIRAL TEST</p> <p>SCORE 1</p> <p>SCORE 2</p> <p>SCORE 3</p> <p>SCORE 4</p> <p>Scoring of the disturbances of drawing in the Archimedes' spiral test.</p> <p>III. Speech disorders</p> <p>15. Dysarthria: fluency of speech (The patient is asked to repeat several times a standard sentence, always the same, for instance: "A mischievous spectacle in Czechoslovakia.")</p> <p>0 = Normal 1 = Mild modification of fluency 2 = Moderate modification of fluency 3 = Considerably slow and dysarthric speech 4 = No speech</p> <p>Score: ...</p> <p>16. Dysarthria: clarity of speech</p> <p>0 = Normal 1 = Suggestion of slurring 2 = Definite slurring, most words understandable 3 = Severe slurring, speech not understandable 4 = No speech</p> <p>Score: ...Dysarthria score: .../8</p> <p>IV. Oculomotor disorders</p> <p>17. Gaze-evoked nystagmus (The subject is asked to look laterally at the finger of the examiner: the movements assessed are mainly horizontal, but they may be oblique, rotatory, or vertical.)</p> <p>0 = Normal 1 = Transient 2 = Persistent but moderate 3 = Persistent and severe</p> <p>Score: ...</p> <p>18. Abnormalities of the ocular pursuit (The subject is asked to follow the slow lateral movement performed by the finger of the examiner.)</p> <p>0 = Normal 1 = Slightly saccadic 2 = Clearly saccadic</p> <p>Score: ...</p> <p>19. Dysmetria of the saccade (The two index fingers of the examiner are placed in each temporal visual field of the patient, whose eyes are in the primary position; the patient is then asked to look laterally at the finger, on the right and on the left; the average overshoot or undershoot of the two sides is then estimated.)</p> <p>0 = Absent 1 = Bilateral clear overshoot or undershoot of the saccade</p> <p>Score: ...Oculomotor movement score: .../6</p> <p>TOTAL ATAXIA SCORE: .../100</p> |
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Table 2 Patients data.

| No. | Age | Sex | Diagnosis | Start of Kampo | Medication | pre ICARS(I II III IV) | post ICARS(I II III IV) | Improvement of symptoms | Start of TMS | pre ICARS(I II III IV) | post ICARS(I II III IV) |
|-----|-----|--------|-----------|----------------|--------------------|--------------------------|---------------------------|-------------------------|--------------|--------------------------|---------------------------|
| 1 | 55 | Female | OPCA | Mar. 2002 | Shinbu-to | 28 (11, 12, 4, 1) | 28 (11, 12, 4, 1) | Dizziness | Feb. 2003 | 27 (12, 11, 3, 1) | 22 (11, 7, 4, 0) |
| 2 | 29 | Female | SCA1 | Jul. 2002 | Shinbu-to | 28 (8, 13, 3, 4) | 28 (8, 13, 3, 4) | Dizziness | Mar. 2003 | 41 (16, 19, 3, 3) | 38 (15, 17, 3, 3) |
| 3 | 76 | Female | CCA | Jul. 2002 | Shinbu-to | 45 (23, 17, 4, 1) | 45 (23, 17, 4, 1) | Dizziness | Mar. 2003 | 46 (24, 17, 4, 1) | 41 (23, 13, 4, 1) |
| 4 | 61 | Male | OPCA | Dec. 2002 | Shinbu-to | 58 (19, 31, 4, 4) | 58 (19, 31, 4, 4) | Dizziness | Jul. 2003 | 80 (32, 38, 6, 4) | 75 (32, 34, 5, 4) |
| 5 | 68 | Male | CCA | Sep. 2003 | Toki-shakuyaku-san | 31 (6, 17, 4, 4) | 30 (6, 16, 4, 4) | Dizziness, Languor | | | |

Table 3 Elements of Medication.

| Medication | Shouyaku | | | | | | | | | | | | | |
|--------------------|-----------|----------|----------|---------|------|--------|----------|-------|------|-------|--------|--------|-------|------------|
| | Shakuyaku | Bukuryou | Soujutsu | Takusha | Toki | Senkyu | Syoukyou | Bushi | Ougi | Keihi | Taisou | Kanzou | Saiko | Choutoukou |
| Shinbu-to | ○ | ○ | ○ | | | | | ○ | ○ | | | | | |
| Ogi-kencyu-to | ○ | | | | | | | ○ | | ○ | ○ | ○ | | |
| Yokukan-san | | ○ | ○ | | ○ | ○ | | | | | | ○ | ○ | ○ |
| Toki-shakuyaku-san | ○ | ○ | ○ | ○ | ○ | ○ | | | | | | | | |

方 法

倦怠感を伴った症例（5）には当帰芍薬散を投与したが，他の4症例には真武湯を投与した。

5例とも漢方薬投与前は経頭蓋磁気刺激法（transcranial magnetic stimulation; TMS）⁶⁻⁸⁾を併用していたが，TMSを3カ月間中止し，漢方治療のみの評価後，真武湯群では再びTMS（1クール20日間）を開始し，真武湯と併用してその効果について検討した。治療評価には international cooperative ataxia rating scale（ICARS）⁹⁾（Table 1）を用いた。

結 果

真武湯を投与した4例では，投与前および投与3カ月後のICARSは39.75 ± 14.57点で変化はみられなかったが，全例でふらつき感が改善した。

倦怠感に対して当帰芍薬散を投与した症例（5）では，ICARSは投与前が31点で投与3カ月後が30点であり，ふらつき感に加え倦怠感が改善した。患者本人が希望しなかったため，以後のTMSの併用は行わなかった。

その後，漢方薬の内服はそのままであったが，症例（2）は杖歩行になり，ICARSは28点から41点に増加。症例（4）は車椅子生活になり，廃用症候群も加わりICARSは58点から80点に増加した。真武湯を

投与した4例では，TMS施行前のICARSは48.50 ± 22.49点で，施行後は44.00 ± 22.29点と有意に低下を示した（p=0.003）（Table 2）。

考 察

遺伝性脊髄小脳変性症の多くは polyglutamine 病とも呼ばれ，polyglutamine の細胞毒性が原因とされている¹⁰⁾。

Watanabe et al. は当帰，芍薬，沢瀉，川芎が培養小脳顆粒細胞において glutamate 誘発の LDH 活性の抑制を認めたと報告している¹¹⁾。また，芍薬の主要成分の paeoniflorin は，片側前脳基底核破壊ラットにおける単純オペラント弁別行動障害を改善させることも報告されている¹²⁾。

一方，抑肝散が有効であったという報告¹³⁾¹⁴⁾もあるが，当帰芍薬散とは茯苓，蒼朮，当帰，川芎が共通している（Table 3）。当帰，川芎，丹参は培養小脳顆粒細胞の glutamine 合成酵素の活性を80%以上抑制する¹⁵⁾。また，川芎を含む川芎茶調散はラット線条体のドパミンを増加させるという報告¹⁶⁾や，パーキンソン病の運動障害に有効であったという報告¹⁷⁾がある。当帰芍薬散50 mg/kg の反復投与により，マウスの垂直および水平運動量を増大させたという報告もある¹⁸⁾。

当帰芍薬散は当帰，芍薬，川芎を含有しており，本研究においても真武湯投与群と比較して ICARS の改善を認め，かつ以後の TMS を必要とせず，有用であった。

TMS では運動失調を改善させて ICARS は低下させるが⁶⁻⁸⁾，頭重感，頭痛や恐怖感などの副作用があるため⁸⁾，ふらつき感や倦怠感等の自覚症状の改善には効果は乏しい。我々は小脳性運動失調症の改善のためには TMS を，ふらつき感のような自覚症状には真武湯，当帰芍薬散の投与を推奨したい。また，両者を併用することにより，より効果が増すものと考えている。

結 論

真武湯や当帰芍薬散は脊髄小脳変性症の自覚症状を改善させると考えた。また，TMS を併用することにより，効果をより上げると考えた。

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Abstract

**Usefulness of Shinbu-to and Toki-shakuyaku-san
for Spinocerebellar Degeneration
- applied with transcranial magnetic stimulation -**

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The usefulness of Shinbu-to and Toki-shakuyaku-san for spinocerebellar degeneration (SCD) was investigated. Subjects comprised five patients with SCD. Patient diagnosis was as follows: 2 cases of cortical cerebellar atrophy (CCA); 1 case of spinocerebellar ataxia type 1 (SCA1); and 2 cases of olivopontocerebellar atrophy (OPCA). All patients were considered to be in the Yin-deficient state "In-Kyo-shou" by Kampo diagnosis. Shinbu-to was administered to 4 patients. Toki-shakuyaku-san was administered to 1 CCA patient with languor. Prior to and after three months of medication, the patients underwent neurological examination using the international cooperative ataxia rating scale (ICARS).

Although the ICARS score did not improve, dizziness was improved in all patients. In addition, languor in the patient taking Toki-shakuyaku-san was improved. Shinbu-to and Toki-shakuyaku-san improved the subjective symptoms of SCD. Transcranial magnetic stimulation (TMS) was performed in conjunction with Shinbu-to administration in 4 patients. ICARS score improved in patients taking Shinbu-to. These data suggest that Shinbu-to together with transcranial magnetic stimulation is effective for treating SCD.

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