Surgical Results of Percutaneous Suction Aspiration and Drainage for Pyogenic Spondylitis

NORIYUKI ANDO, KIMIAKI SATO, MAMORU MITSUKAWA, KEI YAMADA, TORU WAKIOKA AND KENSEI NAGATA

Department of Orthopaedic Surgery, Kurume University School of Medicine, Kurume 830-0011, Japan

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Summary: Forty patients (24 male and 16 female; age 13-87 years, mean 66 years) with pyogenic spondylitis were treated by percutaneous suction aspiration and drainage between January 1997 and September 2007 at Kurume University Hospital. The surgical procedure and transpedicular approach were similar to those used for percutaneous discectomy in the treatment of intervertebral disc herniation. The average postoperative follow-up period was 22.6 months. Two patients had died by the time of the survey, and two had undergone multiple operations. The clinical outcomes were excellent in 12 patients, good in 17 patients, fair in 5 patients, and poor in 6 patients. The response rate (cases with “excellent” or “good” outcomes) was 72.5% (29 patients). Identification of the organism was possible in 26 patients (65%). The most frequently identified organism was methicillin-resistant Staphylococcus aureus (MRSA; 11 cases), followed by methicillin-sensitive Staphylococcus aureus (MSSA; 5 cases) and Escherichia coli (3 cases). Percutaneous suction aspiration and drainage has been demonstrated as an effective means of treating early spondylitis. This procedure is minimally invasive and enables pathogen identification, histopathological diagnosis and even simultaneous treatment. This is the only means of treatment available for patients who cannot tolerate open surgery. This therapy also promises medico-economic advantages by shortening treatment periods and eliminating open surgery.

Key words pyogenic spondylitis, pyogenic discitis, percutaneous discectomy, minimally invasive spinal surgery

INTRODUCTION

The prevalence of pyogenic spondylitis among patients with pyogenic osteomyelitis was reported to be 3.94% by Kulowski [1] in 1963, whereas Waldvogel et al. [2] reported a higher percentage of 19% in 1970. According to a report by Hashizume et al. [3], the incidence of this disease in Japan in 1988-2002 was twice as high as that in 1973-1987. Following recent advances in healthcare technology, the management of infection in the field of spinal surgery has undergone marked changes. Early diagnosis and detection of infection in this field are now possible owing to advances in diagnostic imaging modalities (computed tomography (CT), magnetic resonance imaging (MRI), etc.), and new diagnostic technologies (use of polymerase chain reaction (PCR), etc.). Furthermore, with the increase in the percentage of elderly in the population and in the use of immunosuppressive drugs such as steroids, the number of immunocompromised hosts has been increasing, resulting in an upward trend in the incidence of pyogenic spondylitis. In this article, we present a review of the results of percutaneous suction aspiration and drainage applied to 40 cases at our facility.
CLINICAL MATERIALS AND METHODS

Patients

Forty patients (24 male and 16 female; age 13-87 years, mean 66 years) with pyogenic spondylitis were treated by percutaneous suction aspiration and drainage between January 1997 and September 2007 at our hospital. All of the patients reported back pain, which was severe enough in 16 patients to prevent them from standing or walking. According to the Heusner classification [4], the disease was in Phase I (spinal ache) in 22 patients, Phase II (root pain) in 12 patients, Phase III (weaknesses of the voluntary muscles, sphincters, and sensibilities) in 6 patients, and Phase IV (paralysis) in none of the patients.

The onset of pyogenic spondylitis was classified according to the criteria of Kulowski as acute in 21 patients, subacute in 13 patients, and insidious in 6 patients. The affected vertebral segments were T9-10 in 1 patient, T12-L1 in 7 patients, L1-2 in 8 patients, L2-3 in 9 patients, L3-4 in 8 patients, and L4-5 in 10 patients. Three patients had two affected vertebral segments. Plain radiography, CT, and MRI were performed in all patients for pretreatment evaluation of the spondylitis. Laboratory data, including serum level of C-reactive protein (CRP), white blood cell count, and erythrocyte sedimentation rate (ESR), were obtained in all patients. The bone destruction stage was classified radiographically using the scheme of Griffiths and Jones [5] as early stage (narrowing of the disc space) in 20 patients, destructive stage (bone destruction, collapse of softened vertebrae, and bone proliferation) in 17 patients, and osteosclerotic stage (new bone formation and osteosclerotic changes) in 3 patients.

The most frequently encountered risk factors were diabetes (11 patients), followed by malignancy (8 patients). Thirty-four patients (85%) had at least one risk factor (Table 1). Many patients had received conservative treatment (antibiotic therapy, bed rest, etc.) at a previous medical facility. Thirty-three patients (82.5%) had received antibiotics preoperatively. The mean period from diagnosis to percutaneous suction aspiration and drainage was 10.2 weeks (range, 3-36 weeks). Four of the patients were unsuitable candidates for general anesthesia or major surgery because of poor general condition.

Technique

The surgical approach and procedure were similar to those in percutaneous discectomy performed for the treatment of intervertebral disc herniation. The patient was positioned laterally or prone, on the table, and the skin was prepared and draped. With the patient under local anesthesia, Mayer’s instrument [6], with an outer diameter of 5.4 mm, was inserted toward the intervertebral disc under real-time fluoroscopic guidance. The entry point and angulation of the instrument were determined based on CT findings obtained just before the operation, and the direction and the depth of insertion were confirmed by fluoroscopy during the operation. The affected intervertebral disc was curetted as far as possible with forceps, and the endplate of the vertebral body was removed using a motor-driven shaver. Then, the disc and its surrounding region were irrigated with a large amount (1000-2000 mL) of normal saline. The removed tissue was sent for bacteriologic and histologic examinations. After these procedures, a suction drainage tube (outer diameter, 3-4 mm) and an epidural catheter were inserted into the affected disc space. Suction aspiration was then applied continuously for 3 weeks, and antibiotics (aminoglycosides) were administered directly into the affected disc space through the epidural catheter for 2 weeks. The duration of drainage in the patients surveyed ranged from 7 to 25 days (mean, 16.4 days). For relatively recent cases, serial infusion of physiological saline (2 mL/hr) with a syringe pump was undertaken in view of the recent increase in the prevalence of drug-resistant pathogens. Only physiological saline was infused in 12 patients (30%). In 2 cases where puncture of the thoracic spine was difficult due to the presence of a rib, we adopted a transpedicular approach with Hijikata’s instrument, which has an outer diameter of 3.5 mm [7].

The patients were also treated with intermittent intravenous or peroral antibiotics until remission, as determined by the absence of signs of inflammation.
Average duration of the intravenous antibiotic administration was 3.8 weeks and average duration of the peroral antibiotic administration was 19.9 weeks. The patient was permitted to sit upright on the edge of the bed on the first day after the operation. As soon as relief from back pain was obtained, the patient was allowed to stand and walk with some type of orthosis. In general, patients then wore an orthosis for approximately 6 months.

Evaluation

After the operation, the aforementioned laboratory examinations were repeated every week for 2 months. A paired t-test was employed to determine the statistical significance of differences between the preoperative and postoperative data. Radiographs were obtained every 2 weeks for 3 months. The outcome of the procedure was evaluated at one year or later after the operation as excellent (no limitation of activities of daily living, no pain, no laboratory evidence of inflammation), good (no limitation of activities of daily living, but mild, occasional pain, and no laboratory evidence of inflammation), fair (slight limitation of activities, continuing pain but less than the pretherapy severity), or poor (limitation of activities of daily living, persistent severe pain, no decrease in the inflammation, or need for another operation). The radiographs were assessed using the classification system of Griffiths: kyphotic or lordotic changes were evaluated by measuring only the pathologic area using the Cobb measurement technique and fusion at the infected area. Presence of epidural or psoas abscess was assessed by CT and MRI.

RESULTS

The postoperative follow-up period ranged from 10 to 61 months, with an average of 22.6 months. None of the patients had neurologic or vascular complications attributable to the procedure. By the time of the survey, 2 patients had died. One of these 2 patients was a case of myelodysplastic syndrome, and had died of pneumonia in the 11th postoperative month. The other patient had systemic lupus erythematosus, was on long-term steroid therapy and maintenance dialysis, and had died of meningitis in the 10th postoperative month. There was one patient who needed additional curettage via an anterior approach and bone graft because of poor infection control. In two other patients, infection could only be controlled after several additional sessions of this surgery. These 5 patients were rated as showing poor outcomes. The clinical outcomes were evaluated 15 months, on average, (range, 10-24 months) after the surgery. The clinical outcome was excellent in 12 patients, good in 17 patients, fair in 5 patients, and poor in 6 patients. The total percentage of patients rated as showing an “excellent” or “good” outcome was 72.5% (29 patients).

Identification of the organism was possible in 26 patients (65%). The most frequently isolated organism was methicillin-resistant Staphylococcus aureus (MRSA, 11 cases), followed by methicillin-sensitive Staphylococcus aureus (MSSA, 5 cases), Escherichia coli (3 cases), methicillin-resistant Staphylococcus epidermidis (MRSE, 2 cases), and 1 case each of methicillin-sensitive Staphylococcus epidermidis (MSSE), Staphylococcus capitis, Staphylococcus sanguis, Candida albicans, Bacteroides fragilis and Bacillus species. Histopathological examination of the resected specimens confirmed the diagnosis of acute spondylitis or spondylitis accompanied by chronic inflammation.

All of the patients complained of back pain, which is the most important clinical sign of pyogenic spondylitis. In 35 patients (87.5%), the pain was alleviated soon after surgery. Of the 16 patients who had had difficulty walking due to pain, 10 (62.5%) became able to walk within one week after the surgery.

A significant decrease of serum CRP was observed within 2 weeks of the operation in 38 patients, while serum CRP increased in 2 patients. The average serum CRP was 8.58 mg/dL (range, 0.2-23.46 mg/dL) before the operation, while it was 2.44 mg/dL (range, 0.18-22.82 mg/dL) at 2 weeks after the operation, 2.22 mg/dL (range, 0.36-60 mg/dL) at 4 weeks after the operation, 1.09 mg/dL (range, 0.87-76 mg/dL) at 6 weeks after the operation, and 0.66 mg/dL (range, 0.39-98 mg/dL) at 8 weeks after the operation (Fig. 1). There was a statistically significant difference between the values measured at every time-point and the value measured before the operation ($P<0.0001$). The average peripheral blood white cell count was 8336/mm$^3$ (range, 2300-72000/mm$^3$) before the operation, 5655/mm$^3$ (range, 2470-16400/mm$^3$) at 2 weeks after the operation, and 5036/mm$^3$ (range, 2320-12700/mm$^3$) at 6 weeks after the operation. There was a statistically significant difference between the values at every time-point after the operation and that measured before the operation ($P<0.01$). The average ESR was 84.1 mm/hr (range, 18-130 mm/hr) before the operation, 66.9 mm/hr (range, 10-122 mm/hr) at 2 weeks after the operation, and 43.6 mm/hr (range, 9-120 mm/hr) at 6 weeks after the operation. These parameters showed no significant difference at 2 weeks after the operation.
operation, but the value at 6 weeks was significantly lower as compared to the preoperative value ($P<0.01$).

Radiographic evaluation was also performed at every follow-up visit to the outpatient clinic. After 1 year, the radiologic findings revealed osseous fusion of the intervertebral space in 24 patients (60%), with increased bony sclerosis of the bodies and better definition of the vertebral endplates in the others. No instability was seen in any patient. Postoperative deformity by an angle of 5° or larger was seen in 6 patients, with the mean angle being 13.7° (range, 6°-23°). Twelve patients who had epidural abscess associated with pyogenic spondylodiscitis showed disappearance of the epidural abscess after surgery. Five patients experienced complicating psoas abscess. Two patients had undergone puncture and drainage preoperatively. One patient underwent postoperative puncture and drainage.

Case report (Fig. 2)

79-year-old man with L2-3 pyogenic spondylitis. He had sustained a fall 2 weeks previously and was admitted to a nearby orthopedic hospital. He developed a pre-ileus condition and was admitted to the Department of Internal Medicine of our hospital. Plain radiographs obtained at the time of admission revealed no abnormality, but a fracture was observed by MRI. Three weeks later, the patient showed no alleviation of the lower back pain and developed a fever. At that time, he was treated with intravenous antibiotics, but the symptoms did not improve. A follow-up MRI revealed an epidural abscess within the lumbar spinal canal. We performed percutaneous suction aspiration and drainage. Immediately, the pain was alleviated and inflammatory signs gradually disappeared. The clinical outcome was good.

DISCUSSION

Conservative treatment is the basic approach used for the treatment of pyogenic spondylitis, and antibiotics play a most important role. To select the most suitable antibiotics, identification of the organism is indispensable. When dealing with patients with suspected pyogenic spondylitis, the first action that must be taken is identification of the organism by biopsy, unless sepsis has already developed.

In 1990, Lifeso [8] reported favorable outcomes following incision and curettage of the intervertebral disc alone in 7 of 20 adults with spinal infection, and contended that adequate therapeutic efficacy can be obtained in some cases through partial curettage and decompression alone. In 1990, Onik et al. [9] reported

In regard to the healing processes of pyogenic spondylitis, an experimental study conducted by Fraser et al. [12] demonstrated that the inflammation associated with infection is gradually controlled by vascularization and the formation of granulation tissue from the subchondral bone, leading to spontaneous healing of the affected vertebrae. This suggests that resection of the infected disc and stimulation of bleeding from the subchondral bone led to favorable formation of granulation tissue, and that the accompanying vascularization accelerated the healing of pyogenic spondylitis. In 1997, Haaker et al., [14] reported satisfactory results in 16 patients with lumbar disc infections treated by percutaneous lumbar discectomy without drainage. We, however, think that drainage is absolutely essential for the treatment of this disease.

Based on these previous findings, Nagata (co-author of this paper) and his coworkers [13] began to apply percutaneous suction aspiration and drainage for the treatment of pyogenic spondylitis. In 1998, they reported the use of continuous drainage and intermittent local administration of antibiotics in addition to percutaneous suction aspiration in 23 patients with pyogenic spondylitis. The outcome was excellent in 13 patients, good in 8 patients, fair in 1 patient, and poor in 1 patient. No bone grafts were placed after debridement in this procedure, and spontaneous fusion was obtained in only 9 patients; however, none of the patients showed instability or any marked kyphotic changes in the affected spines. They indicated that the main advantages of the technique were its lower invasiveness as compared with that of open surgery, and the almost immediate symptomatic relief that it provided. Indications for the technique were considered to include the following: 1) no improvement despite the use of antibiotics and immobilization for at least 1 month; 2) presence of only a single affected intervertebral disc; 3) involvement of the lower thoracic or lumbar spine; 4) absence of any major neurological deficit; 5) absence of radiographically documented marked destructive changes of the affected VB. The procedure was considered to be effective for early-stage pyogenic spondylitis.

However, Hanaoka et al. [15] reported in 2006 that percutaneous drainage and continuous drainage resulted in “good” or better outcomes in all of 5 patients with severe pyogenic spondylitis in whom an abscess or marked bone destruction was present, although these patients had been judged as being unsuitable for open surgery because of poor general condition. Their findings suggest that if combined with continuous irrigation, percutaneous drainage may also be useful in cases of severe pyogenic spondylitis. In 1998, Hadjipavlou et al. [16] reported that 21 (75%) of 28 patients responded to percutaneous discectomy and drainage performed via a transpedicular approach. No additional surgery was needed in 13 of the 26 patients who were available for follow-up, and the other patients required additional surgery for reasons such as stenosis, pseudoarthrosis, bone destruction, and a large amount of epidural inflammatory tissue. In view of the fact that the postero-lateral approach was used in previous reports, the relatively poor outcomes reported by Hadjipavlou et al. may be attributable to the difficulty in satisfactory accomplishment of debridement due to the restricted sleeve motion, as the transpedicular approach involves discectomy via the bone marrow. In any event, the best diagnostic test for spondylodiscitis is tissue diagnosis and/or bacteriologic cultures. Reports have shown transpedicular biopsy as being highly effective and safe. Larger bone samples could be collected and the culture positivity rate was as high as about 70% (19/27 patients).

In 2007, Ito et al. [17] and Yang et al. [18] reported the results of percutaneous endoscopic discectomy and drainage (PEED) applied to 15 cases (30 cases in total). Ito et al. conducted a detailed evaluation of pain alleviation using a visual analog scale (VAS, 0-100mm). The averaged pain score on the VAS was 86 before surgery and 25 at 1 wk after the operation. Spinal fusion was obtained in 13 patients (86.7%). According to the report of Yang et al., 13 patients (86.7%) reported immediate relief of back pain following PEED, and 11 patients (73.3%) required no additional surgery. Two patients were diagnosed as having tuberculous spondylitis. This method, enabling macroscopically sufficient debridement, can therefore yield better success rates than percutaneous discectomy and drainage, but it requires special devices such as a scope designed for this purpose.

As described above, several reports have been published on percutaneous operations for the treat-
ment of pyogenic spondylodiscitis (Table 2). As patients increased in age, the percentage of drug-resistant pathogens became higher, but the efficacy of this method of treatment has been maintained and the results were not inferior to those obtained following percutaneous treatment methods reported from other facilities. Three of the patients studied were diagnosed as having tuberculous spondylitis. It is unknown whether or not this treatment is effective against tuberculous spondylitis, because the number of cases reported to date is not large enough. We avoided application of this method to these cases for fear of fistula formation. However, this method seemed to be effective in cases of tuberculous spondylitis where bone destruction was minimal.

Reports of direct drainage for the treatment of epidural abscess or psoas abscess have also been published [19]. However, as seen in our cases and de-

### Table 2

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MSSA; Methicillin–sensitive *staphylococcus aureus*, include oxacillin–sensitive.
MRSA; Methicillin–resistive *staphylococcus aureus*, include oxacillin–resistive.
MRSE; Methicillin–resistive *staphylococcus epidermidis*, include oxacillin–resistive.
MSSE; Methicillin–sensitive *staphylococcus epidermidis*, include oxacillin–sensitive.
scribed in the report by Ito et al., percutaneous suction aspiration and drainage can be effective in the treatment of epidural abscess or psoas abscess. If the disease remains at the cauda equina level, it seems possible to effectively apply this treatment method for up to stage III disease according to the Heusner classification.

According to our current criteria, this method is indicated in the following cases: (1) resistance to conservative therapy (2-3 weeks), (2) involvement of segments at or below the level of the mid and lower thoracic segments, (3) involvement of two segments or less, (4) moderate or less severe bone destruction, (5) absence of abnormal spinal arrangement requiring spinal reconstruction, (6) absence of intense motor paralysis, and (7) cases not suitable for open surgery due to poor general condition. Following the recent increase in the availability of MRI, pyogenic spondylitis is often diagnosed at a relatively early stage. As a result, the number of cases showing intense bone destruction has been decreasing, with a consequent increase in the number of patients indicated for this method of treatment. This method can be applied safely even to the thoracic segments, if used with CT guidance [20].

Application of this method of treatment for early stages of pyogenic spondylitis can minimize destruction of the intervertebral discs and vertebral bodies. It can also suppress the appearance of symptoms arising from intervertebral instability after healing of infection. This method can thus shorten the overall treatment period and is also favorable from the medico-economic point of view.

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Changes in Task-associated Cerebral Blood Induced by Role Lettering: Measurement by Multichannel Near-infrared Spectroscopy

YASUHIRO OKAMOTO*, KIICHIRO MORITA*,**, ATSUSHI YAMAMOTO*, YOUHEI ISHII*, NORIO HARUGUCHI*** AND NAOHISA UCHIMURA**

*Cognitive and Molecular Research Institute of Brain Diseases, Kurume University, **Department of Neuropsychiatry, Kurume University School of Medicine, Kurume 830-0011 and ***Oita Yuai Hospital, Hita 877-0062, Japan

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Summary: Using optical topography (near-infrared spectroscopy: NIRS), relative changes in oxidized hemoglobin (oxy-Hb) were measured before and after the introduction of Role lettering. Tasks performed during measurements included antegrade (from the subject to other persons) and retrograde (from other persons to the subject) mental imaging and writing tasks. All subjects were junior high school students. Relative changes in oxy-Hb were measured before and 3, 6, and 12 months after the start of Role lettering. The region of interest (ROI) was determined based upon the motor cortex region of hand movement and upon relative oxy-Hb changes noted before any Role lettering. For antegrade mental tasks, oxy-Hb increased significantly in right-sided ROI after 3 months; this increase persisted at 1 year. For retrograde mental tasks, oxy-Hb significantly increased bilaterally at 3 months, an effect that also persisted at 1 year. With the antegrade writing task, no significant difference was observed throughout the study; with the retrograde writing task, oxy-Hb level decreased significantly in right lateral ROI after 6 months; the decrease persisted at 1 year. The number of words produced after Role lettering increased significantly in both antegrade and retrograde writing tasks at 1 year, compared with the number before Role lettering. Role lettering thus altered mental activity, particularly in the right hemisphere. Retrograde writing tasks, similar to those employed in the actual practice of Role lettering, reduced right hemispheric function; continuation of the task enhanced performance. Role lettering studies using NIRS may provide useful psychophysiologic indices.

Key words near-infrared spectroscopy, role lettering, right hemisphere, neuroimaging

INTRODUCTION

Writing therapy is often carried out in conjunction with traditional verbal psychotherapy [1-3]. Such writing has enhanced communication within couples, facilitated discovery of forgotten trauma, and promoted self-realization through self-analyzed assignments [1]. Most psychiatric and mental health professionals have experience with some form of writing as a tool for encouraging patients to express feelings and identify stressors [2]. Writing also can help patients to identify areas of conflict in their lives and is a useful technique that complements ongoing counseling for medical and surgical patients [3]. All therapists must deal with patient psychological defenses and resistance during the therapeutic process.
Role lettering shows promise as an effective treatment for problems resulting from such defenses and resistance because it addresses patients’ paradoxical desires for both self-disclosure and confidentiality in therapy sessions, and this therapeutic exercise is useful in promoting objective self-assessment and personal security by relating oneself to others and others to oneself [5]. As bullying and suicide in junior high school students have recently become more frequent in Japan, appropriate preventive measures based on educational psychological methods, including Role lettering, are needed. Role lettering entails a mental recall task, performance, and insight function [5]. In practicing Role lettering, those performing the task voluntarily write down how another person thinks of them, which tends to nurture the objective ego, as described above, presumably by cerebral processing. We therefore consider that investigation of cognitive function is important in understanding the mechanism of Role lettering.

Cognitive function involves serial information processing, in which large amounts of external information are incorporated and integrated for attention, memory, and motivation, leading to responses to the external environment through movement and the autonomic nervous system [6,7]. This cognitive function is very important in social activities, such as human relationships. Furthermore, emotions, such as joy and sorrow, and the affective responses that they induce, are particularly important for interpersonal relations [8-10]. Conditions accompanied by negative emotions, such as deep sorrow and distress, negatively impact interpersonal relations and cause irrational behavior [11]. Near-infrared spectroscopy (NIRS) can non-invasively measure oxidized hemoglobin (oxy-Hb) and reduced hemoglobin in blood vessels at the brain surface using scattered near-infrared light [12-14]. Although spatial resolution is low (2 to 3 cm), the temporal resolution of NIRS (0.1 seconds) is higher than in other cerebral blood flow evaluation methods. The measuring device is relatively compact and portable. In addition, dynamic changes in brain function can be visualized by converting the hemoglobin data to a 2-dimensional image. Suto et al. [15] measured changes in oxy-Hb during a word fluency task, concluding that oxy-Hb measurements can serve as a useful psycho-physiological index reflecting cognitive function. Ishii et al. [16] simultaneously measured oxy-Hb and eye movements using an original method, observing changes in oxy-Hb during an emotionally loaded task performance, and they also suggested that NIRS is a useful tool to investigate emotional cognitive function.

However, the usefulness of Role lettering in biologic evaluation has not been studied and the mechanism is unclear. We therefore non-invasively investigated task-associated relative changes in oxy-Hb by NIRS before and after introducing Role lettering for a period of up to 1 year.

MATERIALS AND METHODS

Subjects

Subjects were 16 junior high school students (age, 12.1±0.8; boys, 13; girls, 3). No subject had a psychiatric illness or motor system disease. No subject had carried out Role lettering prior to session 1; afterward, they performed Role lettering once a week for 12 months at school [5]. All subjects were right-handed and carried out writing tasks with their right hand. The ethics committee of Kurume University approved the present study. Written informed consent was obtained from all subjects and their parents prior to any participation in the study.

NIRS measurements

Relative changes in oxy-Hb were recorded during tasks, using a multichannel NIRS instrument (ETG4000; Hitachi, Tokyo) in frontal (22 channels, Ch) and right and left lateral recording regions (24 Ch each) [16,17]. Tasks performed by subjects during measurements were as follows.

Mental imaging tasks: The subject imaged a verbal thought, ‘once upon a time...’ as a resting state. Old folk tales beginning in this manner are very popular in Japan and were well known to all subjects. The subject then imaged some type of positive affective thought from himself toward 5 persons in different relationship classes (friend, mother, father, teacher, and special friend) as an antegrade task, and then from each of these persons toward himself as a retrograde task, at 30-second intervals. Averaged waveforms for the 5 tasks were measured, and changes in oxy-Hb from the resting state were converted to numeric values every 100 ms. The mean value of oxy-Hb 5 seconds before and 5 seconds after the resting state was considered to be the baseline, and changes in oxy-Hb were observed between tasks and between the baseline. Changes in the area under the waveforms during performance of each task for 30 seconds were also determined [17].

Writing tasks: The subject wrote the once-upon-a-time story to establish a resting state, and ‘from me to five kinds of persons (friend, mother, father, teacher, special friend) as antegrade tasks, and ‘from five kind
of persons (friend, mother, father, teacher, special friend) to me' as retrograde tasks with 30-second resting intervals, respectively. The averaged waveforms in the 5 tasks were measured, and compared with the resting-state. Oxy-Hb level was converted to numerical values every 100 ms [17] and the waveform area during performance of each task (30 seconds) was calculated.

**Regions of interest (ROI) (Fig. 1 and 2)**

In the present study, ROI were evaluated to determine physiologic significance. Motor-related channels were selected based upon the motor effect when the right hand was moving as. Role writing-related channels were also selected during the retrograde Role lettering task at session 1, as shown in Fig. 1. We considered Ch19, 21, 22, and 24 as right recording channels, and Ch6, 8, 9, and 11 as left recording channels; and Ch10, 14, 15 (left frontal), Ch11, 12, 16 (paramedical frontal), Ch13, 17, 18 (right frontal) as front recording channels.

**Statistical analysis**

Oxy-Hb data were examined using one-way repeated measures analysis of variance (ANOVA), with respect to session to evaluate epsilon factors and determine the session effect in each task. A Scheffe test was applied post hoc to identify significant differences between sessions. A probability value lower than 5% was considered to indicate statistical significance. The correlation between oxy-Hb and number of words produced was expressed as Pearson’s product-moment correlation coefficient (r); Bracelet’s t test was used to evaluate statistical significance. Values are presented in the text as the mean ± standard deviation (SD).

**RESULTS**

**Antegrade mental task**

During the antegrade mental task, a session effect upon oxy-Hb in right-sided ROI was apparent in results of one-way repeated ANOVA [F=4.26, p<0.01]. Oxy-Hb was significantly increased in right-sided

![Graph A](image1.png)

**A Moving of right hand**

- **Left**
  - Ch1 to Ch12

- **Right**
  - Ch13 to Ch24

![Graph B](image2.png)

**B Role writing (Retrograde : Before)**

- **Left**
  - Ch1 to Ch12

- **Right**
  - Ch13 to Ch24

*Fig. 1. Identification of regions of interest (ROI). The relative oxy-Hb values was evaluated with the area in each 100 ms. Each dotted bar indicated the averaged oxy-Hb level. A: Relative changes in oxy-Hb upon moving the left and the right hands. B: Relative changes in oxy-Hb during the retrograde writing task before introduction of Role lettering in left lateral and right lateral sides. Each dotted bar indicated the averaged oxy-Hb values. Lines square (□) indicated the channels over an average oxy-Hb values. Closed square (■) indicated the presented ROI. *, p<0.05.*
ROI at 3 months (p<0.05) as compared with that before introducing Role lettering; this effect persisted at 1 year (6 months, p<0.05; 12 months, p<0.05). However, no significant difference in oxy-Hb was noted in left lateral or frontal sites.

Retrograde mental task (Fig. 3)

During the retrograde mental task, a session effect upon oxy-Hb was demonstrated in right lateral ROI [F=12.23, p<0.0001] and left lateral ROI [F=4.06, p<0.01] by one-way repeated ANOVA. In right lateral ROI, oxy-Hb was significantly increased at 3 months (p<0.001) compared with that before the introduction of Role lettering, an effect persisting at 1 year (6 months, p<0.0001; 12 months, p<0.0001). In left lateral ROI, oxy-Hb level increased significantly at 6 months (p<0.05) and 12 months (p<0.05) as compared with the baseline before Role lettering. However, no significant difference in oxy-Hb was found at any frontal sites.

Antegrade writing task

There were no significant differences among sessions during the period of Role lettering over a period of 12 months. The antegrade writing task did not significantly alter oxy-Hb level, suggesting that writing a diary may have little activating effect.

Retrograde writing task (Fig. 4)

During the retrograde writing task, a session effect upon oxy-Hb in right lateral ROI was evident by one-way repeated ANOVA [F=6.80, p<0.001]. Oxy-Hb decreased significantly at 6 months (p<0.01) compared to that before the start of Role lettering, a change that persisted at 12 months (p<0.01). However, no significant difference in oxy-Hb was noted at left lateral or at frontal sites.

Number of words (Fig. 5)

As for number of words, the number increased significantly at 1 year from the number before introducing Role lettering in both antegrade (F=21.53, p<0.0001) and retrograde tasks [F=21.90, p<0.0001].

The number of words in the antegrade task at 1 year after Role lettering correlated negatively with oxy-Hb (r=−0.344, p<0.01) only in right lateral ROI. By channel, the number of words in the antegrade task correlated positively with oxy-Hb in left channel 5 (r=0.525, p<0.05). The number of words in the retrograde task at 1 year after Role lettering correlated negatively with oxy-Hb (r=−0.318, p<0.05) only in right lateral ROI. By channel, the number of words in the retrograde task correlated negatively with oxy-Hb levels (r=−0.606, p<0.05) only in right channel 24.
Fig. 3. Regional relative changes in oxy-Hb during retrograde imaging task before (Pre.) and up to 12 months (M) after beginning Role lettering. Left, selected recordings. Red color indicated the plus levels in oxy-Hb, and blue color indicated the minus levels in oxy-Hb. Right, Oxy-Hb vs. time point. ○, left lateral (LL); ●, right lateral (RL); □, left frontal (LF); ■, right frontal (RF); △, paramedical frontal (PF). *, p<0.05; **, p<0.01; ***, p<0.001.

Fig. 4. Regional relative changes in oxy-Hb during the retrograde writing task before (Pre.) and up to 12 months (M) after beginning Role lettering. Left, subtracted oxy-Hb changes (Subtract 12M from Pre.) - and selected waveforms. Blue color indicated the minus levels. Oxy-Hb was high on both left and right sides. Right, Oxy-Hb vs. time point. ○, left lateral (LL); ●, right lateral (RL); □, left frontal (LF); ■, right frontal (RF); △, paramedical frontal (PF). *, p<0.05.
DISCUSSION

To appreciate the function of Role lettering, the concept of writing therapy must be well understood. Writing therapy has attracted much attention, and writing exercises are often completed as homework assignments for use in conjunction with traditional verbal psychotherapy [1,2]. Writing has been found to increase communication within couples, has aided in the discovery of forgotten trauma, and has encouraged self-realization through self-analysis of assignments [1]. Most psychiatric and mental health professionals have some experience with writing as a tool for enabling patients to express feelings and identify stressors more readily [2]. Writing can be used effectively with patients who are reluctant or embarrassed to speak openly in one-on-one interactions [2]. Thus, expressing one’s thoughts, feelings, and urges in writing transforms primary process activities of the self into secondary processes that are more mature and adaptive to healthy functioning in day-to-day living [4]; however, the biological mechanism of writing therapy is unknown.

Activity related to event-related potentials reflecting cognitive function was detected by NIRS; the affected region may have included the lateral frontal gyrus [17], and the authors indicated that left channel 6 might (Fig. 1,2) be a middle prefrontal region. According to Yamamoto et al. [17] channel 24 may be an inferior frontal region related to imaging [18]. In fMRI studies, the left dorsolateral prefrontal cortex [19], considered to be involved in working memory, was activated during task performance [20]. Activities related to the right hemisphere include those detected during drawing tests [18]. The main difference between Role lettering and writing therapy is the retrograde writing task. On recording during the retrograde writing task, right hemispheric activity before introducing Role lettering was greatly elevated in Ch22 and 24 (See Fig. 1 and 2), with the maximum recorded at Ch24, a relatively frontal location. Before Role lettering practice, no significant correlation was obtained between the number of words and oxy-Hb changes; however, a significant negative correlation was detected between the number of words and oxy-Hb levels (r= −0.606) only in right Ch24 after 12 months. These results indicate that the area in Ch24 may be the most important area for Role lettering practice. A responsive search score for exploratory eye movement has been reported to be a psychophysiological index reflecting interpersonal relations that relates to right hemispheric function [21]. The score is a numeric presentation of the visual field of exploratory eye movement after the subject reports the completion of identifying differences in a visual task. Attitude with latitude is considered of principle importance in interpersonal relationships. Accordingly, asking the subject whether any further difference is present, as opposed to making a simple com-

![Fig. 5. Changes in total number of words. A: Antegrade writing task, before Role lettering (Pre.) and after 12 months (M). B: Retrograde writing task, before Role lettering (Pre.) and after 12 months (M). n = number of words. *** p<0.001.](image-url)
Role lettering, is important for establishing the interpersonal condition from the other person to oneself, as in the retrograde writing task.

The changes in oxy-Hb during the antegrade writing task before Role lettering in right and left ROI were significantly smaller than that during the retrograde writing task. During the antegrade writing task, oxy-Hb did not change significantly over a period of 1 year. The retrograde writing task, however, significantly decreased oxy-Hb at 6 months compared to oxy-Hb before introducing Role lettering; the decrease persisted at 1 year and was detected only in the right recording region. This task most closely resembled the practice of Role lettering, suggesting that the right hemisphere became more weakly activated through training and learning in Role lettering in spite of an increase in the number of words used. This may increase the efficacy of imaging other persons’ thoughts in the retrograde task. Liu et al. [22] reported that the middle frontal area and fusiform gyrus were activated following word training and familiarity with the writing system. Emotion is of fundamental importance in human relationships and determines human behavior. The effects of emotion should be present during Role lettering. It has been reported that the right hemisphere appears to be concerned with emotional processing [23]. Emotional effects have also been studied with NIRS [10,24]. Marumo et al. [24] reported that right lateral prefrontal cortex might be related to negative emotional stimuli and showed gender differences. Furthermore, the right frontal systems showed more activation with novel cognitive strategies and this area is organized principally to process novel challenges [25]. Thus, the decrease in the right oxy-Hb level after Role lettering indicates the possibility that the effect of emotion became weak after practice.

During the antegrade mental task, oxy-Hb was significantly increased at 3 months compared to oxy-Hb before introducing Role lettering; this increase persisted at 1 year. While the increase was detected only in right recording regions at 3 months, it had become bilateral at 1 year. The right hemisphere is related to imagination, while the left subserves speech and logic, suggesting that the right brain is selectively activated by the act of imaging [13,18]. The retrograde mental task also significantly increased oxy-Hb at 3 months compared to oxy-Hb before introducing Role lettering; the increase persisted and became bilateral at 1 year. Additionally, the left-sided component of activation from the retrograde mental task suggests that Role lettering facilitated activation of the left as well as the right hemisphere during that mental task [13].

Further characterization of the active region is necessary, especially for right brain function. Investigation of a larger number of subjects and more detailed analyses of individual subjects are also necessary. It should be considered that the temporal gyrus is associated with emotions and memories, while the insula has been linked to self-recognition and the evaluation of judgment [18]. Thus, structures slightly below the lateral recording regions may have included the temporal gyrus and insula [18]. As the region of the present observed changes in oxy-Hb may be related to the temporal gyrus, more definitive localization by fMRI is necessary during the retrograde writing task.

Finally, Role lettering can help to restore a sense of self-security, patience, and an understanding of how others feel. Oxy-Hb decreased significantly only in right recording regions, suggesting that subjects became more able to objectively observe and describe themselves while thinking about themselves as viewed by other person as they practiced Role lettering. The retrograde writing task may be difficult before practice. Nevertheless, healthy persons are able to perform the task, which initially appears to involve a marked increase in brain activity [18]. Unfamiliar strategies, such as the retrograde writing task before Role lettering practice, may therefore become familiar [25]. Persistent practice may enhance skill in performing the task as the result of familiarity [23,26]. Role lettering should act with other therapeutic techniques used in combination [1,2]. By training and continuation, people become able to readily understand and perform the task, suggesting that plasticity of the cortical network for emotionally related imaging may contribute to adaptations related to Role lettering practice. Role lettering therapy is therefore a useful contribution to transactional analysis therapy.

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REFERENCES

Association between the Transition from Unemployment to Re-employment after Abrupt Bankruptcy and the Depressive Symptoms

KAORI NAGATOMI, TATSUYA ISHITAKE, KUNIO HARA, AKIRA SHIGEMOTO, MICHIKO HOSHIKO, YOSHIASU TSUJI, YOSHIE YAMAGUCHI, HIDEKI TAMAKI, MITSUYO FURUMURA AND JUNKO MURAMOTO

Department of Environmental Medicine, Kurume University School of Medicine, Kurume 830-0011, Japan

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Summary: The study aimed to examine the effects of long-term unemployment and the transition from unemployment to re-employment after abrupt bankruptcy on the mental health of unemployed Japanese. The cases of 96 men and 54 women who were laid off by a large shoemaking company because of sudden bankruptcy in 1998, were examined for one year. The mental health of these individuals was evaluated using a ‘self-rating questionnaire for depression (SRQ-D)’. The respondents were categorized by employment transition status into four groups: (1) still employed full-time, (2) unemployment to full-time employment, (3) unemployment to part-time employment, and (4) still unemployed. The prevalence rate of depressive symptoms in the ‘still unemployed’ group was significantly higher (adjusted odds ratio (OR) = 4.33) than in the still employed group. Moreover, high levels of depressive symptoms were observed in the individuals in the ‘unemployment to part-time employment’ group (adjusted OR = 4.93). There was no significant risk of depressive tendency among individuals in the ‘unemployment to full-time employment’ group. The results suggest that the negative effect of re-employment to part-time employment on depressive symptoms is similar to that in long-term unemployment.

Key words long-term unemployment, re-employment, employment transition, depressive symptoms, unemployment benefits, bankruptcy, part-time employment

INTRODUCTION

During the late 1990s the Japanese economy experienced a severe recession. The number of bankruptcies increased, and the unemployment rate reached a high of 5.4% in 2002. Thereafter, the unemployment rates in Japan decreased to 4.1% in 2006. However, the rate of long-term unemployment (unemployed for more than one year) had increased. In 2005, 33.3% of the unemployed were categorized as long-term unemployed. The number of long-term unemployed individuals increased approximately four fold from 1995 to 2005 [1]. The long-term unemployment rate was higher among adult men, youth (under 34 years), and the elderly (over 55 years) [2]. Many studies have shown the negative effects of unemployment on the physical and mental health and lifestyle of the unemployed [3,4]. Longitudinal studies have revealed that the transition from employment to unemployment is associated with increased psychological distress. Re-employment was noted to have a beneficial effect on psychological well-being [5].
The length of the unemployment period was observed in order to evaluate its effect on the relationship between unemployment and mental health. Long-term unemployment was associated with an increased risk of major depressive episodes [6]. On the other hand, several studies suggested that the prevalence of frequent mental distress was similar in both the short- and long-term unemployed [7]. Long-term unemployment results in severe financial difficulties. Financial resources and financial strain are important factors that determine the well-being of an individual during unemployment. Financial strain is a risk factor for subsequent clinically significant levels of depressive symptoms [8]. Unemployment benefits are an important financial resource for the unemployed. Individuals who underwent a transition from being employed to being unemployed and faced severe financial problems were more likely to experience psychological distress than those who did not [9].

Unemployment benefit systems vary considerably throughout the world in terms of coverage, source of funds, qualifying conditions, benefit amounts, and the duration of coverage. Thus, unemployment protection systems are a possible factor responsible for the different relationships between unemployment and well-being observed in the studies conducted in various countries [10]. In Japan, the benefit period ranges between 90 and 360 days from the first day of unemployment, and the unemployment allowance is decided on the basis of an individual’s age at the time of quitting the job, period of employment insurance, and reason for quitting the job. The unemployment allowance amounts to approximately 50% to 80% of the salary drawn during employment.

Few studies have been conducted on the mental health and well-being of unemployed Japanese. Interviews conducted with unemployed Japanese using the Hello Work system (Japanese public employment security office) revealed that 45.5% of men and 37.9% of women were in a state of depression, and that 54.4% of the men and 41.4% of the women experienced stress caused by financial problems [11]. However, no well-designed studies have been conducted. This study aimed to examine whether the transition from unemployment to re-employment was related to depression among unemployed Japanese.

**METHODS**

**Subjects**

This study involved workers who were laid off by a large shoemaking company in Japan. Figure 1 shows the study design, including the timing of several events and changes in subject number. In April 1998 the company suddenly went bankrupt, and four months later approximately 760 workers, who were over 40 years of age, left the company claiming voluntary retirement. Two months later, 473 of these unemployed individuals organized an association with the aim of exchanging information on re-employment and promoting mutual friendship. The first survey was conducted in May 1999, 12 months after the company declared bankruptcy. We mailed the first questionnaire to all the members of the association; 361 individuals returned the questionnaire, for a response rate of 76.5%. In August 1999, the unemployment benefits were terminated; however, almost half of the members were still unemployed. The second questionnaire was mailed in November 1999, 18 months after the company went bankrupt, i.e. two months after the termination of unemployment benefits. This time, 349 individuals returned the questionnaire; the response rate was 73.5%. The sample used for this study comprised 298 individuals who returned both questionnaires and who were still unemployed or had obtained full-time employment at the time of the first survey. Excluded from the study were 146 respondents who had missing data and 2 respondents who were employed full-time during the first survey but underwent a transition to part-time employment during the second survey. As a result the final study covered a total of 150 individuals consisting of 96 men and 54 women.
Measures

The self-administered questionnaires comprised questions on depression and demographic and employment variables. Depression was assessed using a ‘self-rating questionnaire for depression (SRQ-D)’ [12]. The SRQ-D comprises 18 items with 4 alternative answers, namely, ‘no’, ‘sometimes’, ‘frequently’, and ‘always’ which were assigned the scores of 0, 1, 2, and 3 points, respectively [13]. Of the 18 questions, 6 were dummy variables. According to the diagnostic criteria for depression, a score of 9 points or less was considered to be within the normal range; a score between 10 and 15 as borderline; and a score of 16 points or more, as mild depression. To evaluate the changes of prevalence rate of depressive symptoms according to employment transition status, we dichotomized at 10 points. Scores over 10 points were included in the high SRQ-D score group, and those below (9 points or less) were considered the normal group. The employment variables considered were the re-employment situation, employment status, age at the time of joining the company, and age at the time of being laid off. The re-employment situation was subdivided into four categories; working in a new full-time job, working in a part-time job, temporarily employed, and still unemployed. The job classification was the type of job they had performed in the shoemaking company, i.e., manual or non-manual work. The duration of service was calculated as the difference between the age at the time of joining the company and that at the time of being laid off; it was dichotomized at 30 years.

Statistical analysis

Employment transitions were categorized into the following four groups: (1) found a new full-time job at the time of the first survey and remained employed until the time of the second survey (‘still employed full-time’), (2) unemployed at the time of the first survey and employed full-time at the time of the second survey (‘transitioned from unemployment to full-time employment’), (3) unemployed at the time of the first survey and employed part-time at the time of the second survey (‘transitioned from unemployment to part-time employment’), and (4) unemployed at the time of both surveys (‘still unemployed’). In the absence of a control group that had not experienced unemployment, we used individuals in the ‘still employed full-time’ group as a reference. First, a chi-square test was conducted to compare the baseline characteristics among the four employment transition groups, following which depression tendencies at the time of the first survey were compared using the demographic variables. In order to examine the relationship between employment transition and depressive symptoms, a multiple logistic regression analysis was performed. Depressive tendencies at the time of the second survey were applied to the outcome variable. The age at the time of the first survey, gender, job classification, duration of service, and depression tendency at the time of the first survey were adjusted. The odds ratio (OR) and 95% confidence intervals were presented. Data analyses were performed using SPSS 11.0J.

Ethical considerations

The subjects were provided with oral and written explanations of the purpose, methods, and contents of the investigation. In addition, they were also informed that they had the right to refuse participation at any time, that the results of the investigation would be maintained confidential and used only for this study. However, this study was not approved by the Institutional Review Board (IRB) of Kurume University because our IRB was not established until 2002, well after the study had begun.

RESULTS

Table 1 presents the characteristics of the subjects at the time of the first survey. Individuals who were employed full-time at the time of both the surveys were younger than those in the other employment groups; however, no significant difference was found between these groups. Furthermore, men were more likely to have found a new full-time job than women. The sex ratios showed significant differences among the four groups. The duration of service was shorter in the ‘still employed full-time’ group than in the other groups.

The mean SRQ-D scores were higher in the ‘from unemployment to full-time employment’ group and lower in the ‘still employed full-time’ group. However, the differences were not significant. The number of participants who were categorized in the mild depression (over 16 points) group were few (5.3% in the first survey; 8.0% in the second survey); hence, we dichotomized at 10 points, with scores of 10 or more comprising the high SRQ-D score group, and those 9 points or less comprising the normal SRQ-D score group. The prevalence rate of high SRQ-D scores (over 10 points) was higher in the ‘unemployment to part-time employment’ group than in the other groups. However, no significant differences were observed between the groups.

Table 2 shows the prevalence rates of high SRQ-D
scores in the first survey and the second survey across different independent variables. Overall, 28.0% of the respondents in the first survey and 26.7% in the second survey were believed to experience depressive symptoms. Higher tendencies toward depression were found in the higher age groups than in the lower age groups. In both surveys, the prevalence rate of high SRQ-D scores in women was less than men. Individuals who had worked for over 30 years had a greater tendency to depression. The difference of prevalence rate for duration of service in the second survey increased. Individuals who were unemployed during the first survey showed a greater tendency to depression than those who were employed at that time. Moreover, the prevalence rate of high SRQ-D scores was lower among individuals who were employed full-time than among those who were employed part-time or were unemployed in the second survey. The ORs for each independent variable were not significant.

The relationships between employment transition status and depressive symptoms are illustrated in Table 3. The ORs were calculated after adjusting for age, sex, job classification before bankruptcy, duration of service, and depression tendency at the time of the first survey. Individuals in the ‘unemployment to part-time employment’ (adjusted OR 4.93, 95% CI 1.01-24.08) and ‘still unemployed’ (adjusted OR 4.33, 95% CI 1.03-18.10) groups reported higher depressive tendencies as compared to those in the ‘still employed full-time’ group. However, no significant difference was observed between the ‘unemployment to full-time employment’ group and the ‘still employed full-time’ group.

DISCUSSION

The aim of this study was to examine the relationship between transition from unemployment to re-employment and tendency toward depression among unemployed Japanese. Continued unemployment was a risk factor for depressive symptoms. At the time of the first survey, differences in the rates of high SRQ-D scores between the unemployed and re-employed individuals were not significant. However, six months later, the rate of high SRQ-D scores among the unemployed increased. At the time of the second survey, the
### TABLE 2.
*Prevalence rates of high SRQ-D score (over 10 points) across different independent variables according to logistic regression analysis*

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<tr>
<td>Duration of service</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>within 30 years</td>
<td>25.0</td>
<td>1.00</td>
<td>–</td>
<td>17.5</td>
</tr>
<tr>
<td>over 30 years</td>
<td>29.7</td>
<td>1.27</td>
<td>0.55 - 2.92</td>
<td>0.577</td>
</tr>
<tr>
<td>Job classification before bankruptcy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>manual work</td>
<td>27.3</td>
<td>1.00</td>
<td>–</td>
<td>27.3</td>
</tr>
<tr>
<td>non-manual work</td>
<td>29.0</td>
<td>1.09</td>
<td>0.46 - 2.60</td>
<td>0.850</td>
</tr>
<tr>
<td>Employment status at the first survey</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>full-time employment</td>
<td>23.5</td>
<td>1.00</td>
<td>–</td>
<td>14.7</td>
</tr>
<tr>
<td>unemployment</td>
<td>29.3</td>
<td>1.35</td>
<td>0.56 - 3.28</td>
<td>0.510</td>
</tr>
<tr>
<td>Employment status at the second survey</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>full-time employment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>part-time employment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>unemployment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OR = odds ratio, 95% CI = 95% confidence interval

### TABLE 3.
*Relationships between employment transitions and depressive symptoms revealed by the second survey based on multiple logistic regression analysis*

<table>
<thead>
<tr>
<th>Employment transitions</th>
<th>Prevalence rate of high SRQ-D score (%)</th>
<th>OR*</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Still full-time employed</td>
<td>14.7</td>
<td>1.00</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>From unemployment to full-time employment</td>
<td>26.9</td>
<td>2.52</td>
<td>0.42 - 15.11</td>
<td>0.313</td>
</tr>
<tr>
<td>From unemployment to part-time employment</td>
<td>35.5</td>
<td>4.93</td>
<td>1.01 - 24.08</td>
<td>0.049</td>
</tr>
<tr>
<td>Still unemployed</td>
<td>28.8</td>
<td>4.33</td>
<td>1.03 - 18.10</td>
<td>0.045</td>
</tr>
</tbody>
</table>

OR* are adjusted for age, sex, job classification before bankruptcy, duration of service, and depression status at the first survey (SRQ-D scores within 9 points or not).
duration of unemployment exceeded one year, which qualified as long-term unemployment. Unemployment benefits were terminated during the period between the first and second surveys. It was assumed that the financial situation among the unemployed had worsened. The effects of financial strain on mental health and well-being among unemployed individuals have been reported in previous studies [8,14]. Furthermore, the present study suggests that negative effects on mental health were prevalent in individuals who remained unemployed. Interestingly, individuals who were employed part-time and those who remained unemployed showed similar results. Previous studies suggested that re-employment decreases the levels of psychological stress [5,8]. However, the results of this study revealed that the risk of depressive tendency among part-time re-employed individuals was similar to that in individuals who were still unemployed. A study conducted on white collar civil servants who experienced job transitions or lay-offs due to privatization suggests that insecure re-employment and unemployment after privatization resulted in an increase in minor psychiatric morbidity [15]. In general, part-time employment was considered to be more insecure than full-time employment. The results of previous studies on psychological stress in individuals who were employed part-time and full-time were inconsistent. Most studies revealed that temporary rather than permanent employment resulted in higher psychological distress [16]. On the other hand, some studies indicated that part-time employment was less stressful than full-time employment [17].

In Japan, the gap between permanent and temporary employment is wide. The advantage of temporary employment lies in the fact that it allows individuals to choose work that suits their lifestyle. However, it has several disadvantages such as low pay, insufficient welfare programs, job insecurity, difficulties in shifting to permanent employment, and fewer opportunities to develop individual skills. Thus far, no study has been able to clarify the state of the mental health and well-being of part-time workers. More than half of the unemployed individuals in this study expressed a preference for permanent as opposed to part-time employment; however, less than half of these requests were fulfilled. Moreover, with an increase in the duration of prolonged unemployment, the rate of part-time re-employment increased. Further, it was noted that selectiveness in the choice of permanent employment resulted in long-term unemployment [18]. The results of this study revealed that the depression scores at the time of the first survey were high in the group that went from unemployment to part-time employment. Although various studies have examined the effects of employment transitions and unemployment on an individual’s health, none have classified the subjects according to employment type. Furthermore, the results of this study suggest that it is necessary to take into consideration the differences in re-employment status when studying the health of unemployed and re-employed individuals.

We hypothesize that both long-term unemployment and re-employment to part-time jobs cause depressive symptoms. However, we must consider the opposite causal relation, in which depressive symptoms affect re-employment condition. Previous studies revealed that high levels of distress predict subsequent unemployment [19,20] and that psychological or physical health problems reduce the chances of finding a new job [21]. It is possible that individuals who were vulnerable to depression found it difficult to make the transition from re-employment to full-time employment. We assessed the depressive symptoms at the baseline; however, no information about the history of mental illness was gathered. Moreover, mental health and the re-employment situation may be affected by psychological factors. For instance, control beliefs [22], social support [23], and coping strategies [24] are related to the mental health and well-being of the unemployed.

Several methodological issues should be considered when interpreting these results. First, we assumed that employment transition was accompanied by a change in the financial status of an individual. However, information regarding actual financial difficulties, such as changes in the household income, was not obtained. This survey required respondents to provide their names; therefore, in the interest of privacy, we did not include data regarding the financial situation of individuals. Moreover, previous studies have suggested that the health status of unemployed individuals was related more to perceived financial strain than to actual financial difficulties [10]. Second, previous studies have reported the effects of sex and age differences on the relationship between employment transition and financial difficulties [8]. The state of being unemployed and not receiving unemployment benefits had a higher impact on the mental health of men than that of women [9]. Some women desired part-time employment because of housekeeping activities; therefore, the effects of part-time employment on mental health were moderated. However, due to a low response rate, our sample size was insufficient. Thus, we could not examine the differences in the effects of depres-
tion based on sex and age. Third, we used individuals in the ‘still employed full-time’ group as a reference because we could not determine which individuals continued working for the shoemaking company. Several studies have shown the harmful effects of lay-offs or downsizing on employees. Individuals who continue to work in a company conducting large-scale downsizing and witness the lay-off of friends and co-workers tend to feel insecure about their job [25]. Job insecurity and short-term unemployment are equally harmful to the mental health [26]. Last, since a comparison between the respondents and non-respondents could not be conducted, it is unclear whether the 150 respondents who participated in this analysis were representative of all the members of the association. In addition to this, we must consider the effect of shift work on mental health because there is the possibility of exposure to shift-work in the individuals with part-time work [27].

Despite these limitations, the results of this study are valuable. This is the first report on the relationship between insecure jobs and mental health among unemployed Japanese. It should be noted that although the unemployment rate is currently being maintained at a low level, the number of long-term unemployed individuals is increasing. Depression during unemployment affects subsequent employment [19,20]. The suicide rate in Japan is rapidly increasing, and unemployment is one of the causes of suicide. However, the relationship between unemployment, depression, and suicide is not clear. Further studies concerning the relationship between insecure jobs and mental health are required.

REFERENCES

22. Ginexi EM, Howe GW, and Caplan RD. Depression and control beliefs in relation to re-employment: what are the
Factors for Drop-out Psychiatric Treatment in Patients with Substance-related Disorders

NAOKO MASAKI*** AND KOJI TOYOMASU*

*Institute of Health and Sports Science, Kurume University, Kurume 839-8502 and **Japanese Red Cross Hiroshima College of Nursing, Hiroshima 738-0052, Japan

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Edited by NAOHISA UCHIMURA

Summary: We studied 199 inpatients and outpatients at a public psychiatric hospital to clarify the factors related to outcome following psychiatric care for substance-related disorder (SRD), and we discuss approaches for more effective community care in the future. The percentage of patients who discontinued treatment was 33.7%, suggesting that creation of a follow-up system for continuing outpatient care is an urgent task. Women were 35% more likely higher to discontinue treatment than men. Those with solvent dependence were 12% and 7.32 times more likely, respectively, to discontinue treatment than those with alcohol dependence. Those without complications were 2.24 times more likely than those with complications to discontinue treatment. Divorced patients were 18% and 6.35 times more likely, respectively, to discontinue treatment than married patients. There is insufficient support for patients with solvent dependence, and we observed that patients tended to have little motivation to stop using drugs or alcohol until physical complications occurred. Among the many divorced patients, desire for treatment was weak following breakdown of the family. The present findings suggest the importance of comprehensive efforts to treat substance use disorder at specialist medical institutions.

Key words substance-related disorder, treatment discontinuation, dependence, psychiatric treatment

INTRODUCTION

Patients with substance-related disorder (SRD, dependence) in Japan tend to have psychotic manifestations, as seen with amphetamines or organic solvents, and tend to be socioeconomically disadvantaged. Thus dealing with SRD involves major issues [1]; treatment tends to be difficult and environmental influences can have an important effect on patient mental health and welfare. Given this situation, we consider that the problem of SRD requires development of appropriate mental health and welfare policies to be applied on a nationwide scale, with large roles to be played by specialist psychiatric care facilities. The spread of dependence among young people suggests the importance of school health and preventive education programs starting during puberty [2,3].

In this study we attempt to clarify the factors related to outcome following psychiatric care for SRD, and discuss the best approaches to community care.

METHODS

Subjects

Subjects were 199 people treated for SRD involving alcohol or drugs who could be followed, from among patients who received inpatient or outpatient treatment between January 1996 and December 2000 at a public psychiatric hospital.

Survey content

The 199 subjects were followed from medical
records, from which patient profile, treatment status, and present outcome were confirmed. The follow-up period was a maximum of 6 years and minimum of 2 years. Factors related to discontinuing treatment and odds ratios for these were obtained for 67 people who discontinued treatment and 53 people who continued treatment as outpatients, and χ² tests were conducted. The subjects were observed at a single hospital, so those who changed hospitals could not be followed. Therefore, in analyzing the risk of discontinuing treatment for patients who dropped out of treatment and those who completed treatment or were continuing treatment as outpatients, patients who transferred to other hospitals were excluded from the analysis. SPSS Ver. 7 for Windows and FSTAT were used in the statistical analysis. A P value of less than 0.05 was taken as the criterion for statistical significance.

For ethical reasons, the survey forms were completed by each patient’s primary physician and primary mental health professional using the patient’s medical records. This was an anonymous numerical analysis based on retrospective collection of medical information.

RESULTS

Subjects’ basic attributes are shown in Table 1. There were more men than women, with a male: female ratio of 83.9:16.1. Nearly half the subjects were in the age range of 40-59 years, and many were in their prime working years. The most frequent occupational status was unemployed (34.2%), followed by com-

<table>
<thead>
<tr>
<th>No. people</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
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</tr>
<tr>
<td>Female</td>
<td>32  (16.1)</td>
</tr>
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<table>
<thead>
<tr>
<th>Age</th>
<th>No. people</th>
<th>%</th>
</tr>
</thead>
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<tr>
<td>≤19 y</td>
<td>12 (6.0)</td>
<td></td>
</tr>
<tr>
<td>20-29 y</td>
<td>23 (11.6)</td>
<td></td>
</tr>
<tr>
<td>30-39 y</td>
<td>38 (19.1)</td>
<td></td>
</tr>
<tr>
<td>40-49 y</td>
<td>49 (24.6)</td>
<td></td>
</tr>
<tr>
<td>50-59 y</td>
<td>48 (24.1)</td>
<td></td>
</tr>
<tr>
<td>60-69 y</td>
<td>23 (11.6)</td>
<td></td>
</tr>
<tr>
<td>70-79 y</td>
<td>5  (2.5)</td>
<td></td>
</tr>
<tr>
<td>≥80 y</td>
<td>1  (0.5)</td>
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</tr>
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<tr>
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<th>%</th>
</tr>
</thead>
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<tr>
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</tr>
<tr>
<td>Farmer</td>
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<td></td>
</tr>
<tr>
<td>Other</td>
<td>31 (15.6)</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>68 (34.2)</td>
<td></td>
</tr>
<tr>
<td>Self-employed</td>
<td>15 (7.5)</td>
<td></td>
</tr>
<tr>
<td>Student</td>
<td>3  (1.5)</td>
<td></td>
</tr>
<tr>
<td>Day laborer</td>
<td>4  (2.0)</td>
<td></td>
</tr>
<tr>
<td>Part-time worker</td>
<td>9 (4.5)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>25 (12.5)</td>
<td></td>
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<table>
<thead>
<tr>
<th>Marital status</th>
<th>No. people</th>
<th>%</th>
</tr>
</thead>
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<td>Married</td>
<td>82 (41.2)</td>
<td></td>
</tr>
<tr>
<td>Never married</td>
<td>72 (36.2)</td>
<td></td>
</tr>
<tr>
<td>Divorced</td>
<td>29 (14.6)</td>
<td></td>
</tr>
<tr>
<td>Widowed</td>
<td>2  (1.0)</td>
<td></td>
</tr>
<tr>
<td>Common-law marriage</td>
<td>1 (0.5)</td>
<td></td>
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<tr>
<td>Unknown</td>
<td>15 (6.5)</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Purpose of hospitalization (symptoms on admission)</th>
<th>No. people</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment for dependence</td>
<td>80 (40.2)</td>
<td></td>
</tr>
<tr>
<td>Emergency hospitalization for psychotic state</td>
<td>65 (32.7)</td>
<td></td>
</tr>
<tr>
<td>Physical treatment</td>
<td>4  (2.0)</td>
<td></td>
</tr>
<tr>
<td>Place to stay</td>
<td>2  (1.0)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1  (0.5)</td>
<td></td>
</tr>
<tr>
<td>No hospitalization</td>
<td>47 (23.6)</td>
<td></td>
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<table>
<thead>
<tr>
<th>Substance of dependence</th>
<th>No. people</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>130 (65.3)</td>
<td></td>
</tr>
<tr>
<td>Stimulants psychiatric disease</td>
<td>35 (17.6)</td>
<td></td>
</tr>
<tr>
<td>Organic substance psychiatric disease</td>
<td>20 (10.1)</td>
<td></td>
</tr>
<tr>
<td>Drug dependence</td>
<td>14 (7.0)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complications</th>
<th>No. people</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>105 (52.8)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>85 (42.7)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>9  (4.5)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alcohol treatment program</th>
<th>No. people</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participation</td>
<td>58 (29.1)</td>
<td></td>
</tr>
<tr>
<td>No participation</td>
<td>134 (67.3)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>3  (1.5)</td>
<td></td>
</tr>
<tr>
<td>Not indicated</td>
<td>4  (2.0)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Episode that triggered dependence status</th>
<th>No. people</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>79 (39.7)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>83 (41.7)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>37 (18.6)</td>
<td></td>
</tr>
</tbody>
</table>
company employee (19.1%). Marital status was married for 41.2% of subjects, never married for 36.2%, and divorced for 14.6%.

Treatment status is shown in Table 2. The most common purpose of hospitalization was treatment for dependence (40.2%), followed by emergency hospitalization for a psychotic state in 32.7%. The substance of dependence was alcohol in the majority of cases (65.3%), followed in order by stimulants and organic solvents. Complications were present in 52.8% of cases. The most common complicating condition was liver disease (34.6%), followed by diabetes mellitus (9.5%), gastric resection, tuberculosis, and cardiovascular disease, in that order.

Participation in an alcohol treatment program was reported for 29.1%, and no such participation was reported for 67.3%. In 39.7% of cases there was an episode that led to the dependence, and in 41.7% there was no such episode.

The post-treatment course is shown in Table 3. Of all subjects, 87.9% did not participate in a self-help group, while 8.0% did. The outcome was discontinuation of treatment in 33.7% of cases, outpatient treat-

### TABLE 3.

<table>
<thead>
<tr>
<th></th>
<th>No. people</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participation in self-help group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16 (8.0)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>175 (87.9)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>8 (4.0)</td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient treatment</td>
<td>53 (26.6)</td>
<td></td>
</tr>
<tr>
<td>Hospital transfer</td>
<td>47 (23.6)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>9 (4.5)</td>
<td></td>
</tr>
<tr>
<td>Discontinuing treatment</td>
<td>67 (33.7)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Admission to a facility</td>
<td>4 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Rehospitalization</td>
<td>3 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Treatment completed</td>
<td>5 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (3.0)</td>
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</tr>
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</table>

### TABLE 4.

Discontinuing treatment and related factors

<table>
<thead>
<tr>
<th></th>
<th>Drop out n=67</th>
<th>Continuing outpatient treatment n=53</th>
<th>OR (95%CI)</th>
<th>( \chi^2 ) test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>54 (80.6)</td>
<td>45 (84.9)</td>
<td>1.00</td>
<td>P=0.537</td>
</tr>
<tr>
<td>Female</td>
<td>13 (19.4)</td>
<td>8 (15.1)</td>
<td>1.35 (0.516-3.556)</td>
<td></td>
</tr>
<tr>
<td>Disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol dependence</td>
<td>42 (62.7)</td>
<td>41 (77.4)</td>
<td>1.00</td>
<td>P=0.033</td>
</tr>
<tr>
<td>Stimulants dependence</td>
<td>8 (11.9)</td>
<td>7 (13.2)</td>
<td>1.12 (0.371-3.358)</td>
<td></td>
</tr>
<tr>
<td>Paint thinner dependence</td>
<td>15 (22.4)</td>
<td>2 (3.8)</td>
<td>7.32 (1.574-34.046)</td>
<td></td>
</tr>
<tr>
<td>Drug dependence</td>
<td>2 (3.0)</td>
<td>3 (5.7)</td>
<td>0.65 (0.103-4.099)</td>
<td></td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>28 (41.8)</td>
<td>34 (64.2)</td>
<td>1.00</td>
<td>P=0.034</td>
</tr>
<tr>
<td>No</td>
<td>35 (52.2)</td>
<td>19 (35.8)</td>
<td>2.24 (1.057-4.734)</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>28 (41.8)</td>
<td>30 (56.6)</td>
<td>1.00</td>
<td>P=0.039</td>
</tr>
<tr>
<td>Never married</td>
<td>23 (34.3)</td>
<td>19 (35.8)</td>
<td>1.30 (0.585-2.877)</td>
<td></td>
</tr>
<tr>
<td>Divorced</td>
<td>13 (19.4)</td>
<td>2 (3.8)</td>
<td>6.96 (1.441-33.653)</td>
<td></td>
</tr>
<tr>
<td>Widowed</td>
<td>0 (0.0)</td>
<td>1 (1.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*: P<0.05
ment in 26.6%, and transfer to a different institution in 23.6%.

Only 3 patients were rehospitalized. Therefore, no analysis of rehospitalization was done. Some of the transferred patients may have been rehospitalized, but they could not be followed. With regard to past hospitalizations, this was the first hospitalization for 46.2% of patients, second for 30.1%, third for 5.0%, and fourth or subsequent for 7.5%.

The odds ratios for discontinuing treatment and related factors are shown in Table 4. The relative risk of discontinuing treatment was 1.35 for women as compared with men. The relative risk for discontinuing treatment was 7.32 higher for solvent dependence than for alcohol dependence, and the risk of discontinuing treatment was 2.24 times higher for patients without complications than for those with complications. Divorced patients were 6.35 times more likely to discontinue treatment than married patients.

DISCUSSION

Patients with substance-related disorders are often socioeconomically disadvantaged, and given that no effective drug therapy has yet been established, one strongly senses that these patients have tended to be neglected by medical institutions [4].

In psychiatric hospitals it is often said that in the clinical setting two types of patients are difficult to treat and cause the medical staff distress: those with personality disorders and those with substance dependence [5]. Thus the impression exists that dependence tends to be complex and difficult.

The aim of the present study was to elucidate the current status and outcome of treatment based on information that could be obtained from medical records of psychotropic substance abusers, and to examine the factors related to discontinuation of treatment.

Patient characteristics

The subjects of this study included more men than women. The majority were aged 40-59 years, in the prime of their working life, suggesting that substance abuse has a large socioeconomic impact. This points out the importance of coordination with the occupational field, and in the case of male patients, the need for support for the patient’s wife and other women around him.

The most commonly abused substance was alcohol, so it will important to create a system for education, prevention, early detection, and early treatment with regard to problem drinking itself.

More than half of alcohol-dependent subjects, 52.8%, had complications, suggesting the importance of coordination with medical treatment in cases of alcohol or other substance dependence.

Participation in an alcohol treatment program was low, at 29.1%. The patient’s desire to stop drinking (or stop taking drugs) is an essential condition for treatment in specialized treatment wards, which is a high hurdle if the patient does not recognize substance abuse as a disease.

An episode that triggered the dependence was reported in 39.7% of cases, but the specific details were unknown for many patients. In the future it will be necessary to achieve a better understanding of such episodes in patients’ family and workplace relations. Various factors including economic problems and family relations are complexly intertwined in dependence [7], and future analysis of these factors is anticipated.

Post-treatment status

Most of the patients, 87.9%, did not participate in a self-help group. Information from a self-help group was received regularly in the alcohol treatment program, and self-help group participation was also supported during hospitalization. However, few patients participated in a self-help group after leaving the hospital. Regular hospital visits, taking anti-alcohol medication, and participation in a self-help group are targeted as three principles for discontinuing alcohol [6], and support for these behavioral changes is considered important.

The outcome was discontinuation of treatment in 33.7% of cases and discontinuation of outpatient visits in 26.6%. To prevent discontinuation of treatment and encourage regular hospital visits it is important to conduct follow-up after discharge by telephone or other means for those who discontinue treatment. Doing so requires that a relationship of trust be established during hospitalization and that a system be created to obtain consent to continue contact after hospital discharge [7,8]. One of the authors has worked as a mental health and welfare professional in the hospital where these patients were treated, and has noted that patients who discontinue treatment often called for counseling even after they had been discharged. In the future it will be necessary for specialized hospitals to provide this kind of in-depth support.

Treatment discontinuation and related factors

Among the patients who discontinued treatment, there were more patients with solvent or amphetamine dependence than alcohol dependence, more people who
had no complications, and more who were divorced or never married.

Although the difference between the sexes was not significant, more women than men discontinued treatment. Women with dependence are said to receive little support from men, and in many cases they have complex problems [5]. Among women with dependence, cases are seen that involve a complex mix of problems involving money and relationships with their partner. When the present author provides support as a social worker to a woman with dependence, the support is provided in cooperation with a female social worker or case worker from a social welfare office. More support is needed from specialist hospitals for women’s self-help groups, and it will be important to strengthen coordination with welfare policy.

No statistical relation was seen between employment and risk of discontinuing treatment, but the number of unemployed subjects (34.2%) is a major issue. Intervention at an early stage to support people with dependence before they become unemployed is important.

Psychiatric hospitals are always faced with the question of determining the extent to which people with solvent or amphetamine dependence are suited to treatment and how far the criminal justice system should be applied [4]. The current trend appears to favor punishment of problem behaviors and treatment for dependence. From the viewpoint of those providing treatment it is desirable to develop a treatment system while working in coordination with the judiciary.

The proportion of patients without complications who discontinue treatment is probably higher because those who require internal medical or surgical treatment feel that they must continue. In the future it will also be necessary to observe patients with relation to disease duration. People have little insight into dependence as a disease, and in fact refuse to recognize it as such. For that reason, it is necessary to ensure that people with dependence recognize their illness, and so it is said to be essential that they have an experience of “hitting bottom.” In alcohol treatment programs each person’s laboratory test values are monitored by a physician, who then explains them to the patient. This is an opportunity for the physician and patients to exchange views and for the patient to recognize the physical changes that are occurring. In the future we would like to assess behavioral changes after such programs.

Many of the divorced or never-married patients discontinued treatment. Family relations are said to have a large effect on people with dependence [6], suggesting that patients whose family relations have become tenuous because of their problem behavior have difficulty continuing treatment [9]. Outcomes may differ if treatment interventions can be made before family relations break down. What kinds of intervention methods are effective for behavioral change at that stage is a question we would like to investigate in the future.

There were limits in the present analysis because the subjects were observed from records at a single hospital, and rehospitalizations and treatment discontinuation could not be assessed in patients who changed hospitals.

In the present study the post-therapy course was investigated in 199 inpatients and outpatients at a public psychiatric hospital to clarify treatment discontinuation and related factors following psychiatric treatment for SRD, and to consider the best approach for community care in the future. The treatment discontinuation rate was 33.7%, indicating that follow-up of continuing outpatient treatment is an urgent issue. Risk of discontinuing treatment was 35% higher in women than in men, and closer support is therefore thought to be needed for women. Risk of treatment discontinuation was 7.32 times higher for solvent dependence than for alcohol dependence. Support for people with solvent dependence is insufficient, and various arrangements such as linking these patients with a Drug Addiction Rehabilitation Center or other self-help groups are desirable. Risk of discontinuing treatment was 2.24 times higher in those who did not have complications compared with those who had complications. We observed that it was difficult for patients to find positive motivation to stop alcohol or drugs until physical symptoms appeared. Those who were divorced were 6.35 times more likely, respectively, to discontinue treatment than those who were married. Decreased desire for treatment accompanying breakdown of family ties is seen in the high number of divorces. Support for the family before that point is reached is important.

These findings suggest that comprehensive efforts designed to encourage continuation of outpatient treatment are important for support of people treated for SRD at specialist medical institutions.

REFERENCES


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The Interaction between Female Sex Hormone Receptors and Osteopontin in a Rat Hyperoxaluric Model

JIRO MIYAJIMA, TOKUMASA HAYASHI, KOUJIRO SAITO, SHIZUKA IIDA AND KEI MATSUOKA

Department of Urology, Kurume University School of Medicine, Kurume 830-0011, Japan

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Summary: It is well known that the incidence of urinary stones is higher in men than women. Although it is believed that the lower incidence of urinary stones in women is due to a protective effect of estrogen, the mechanisms remain unclear. To clarify the relation between female sex hormones and stone matrix protein, we examined the interaction of estrogen receptor-α (ERα), estrogen receptor-related receptor-α (ERRα), and stone matrix protein osteopontin (OPN) in a rat hyperoxaluric model and in primary cultured rat kidney cells. Adult female Wistar rats were divided into 6 groups. Groups 1 and 4 consisted of normal females, Groups 2 and 5 consisted of ovariectomized females, and Groups 3 and 6 consisted of ovariectomized females receiving female sex hormone supplements. Groups 1-3 were administered distilled water, while groups 4-6 were administered 0.5% ethyleneglycol (EG). Moreover, rat kidney primary cultured cells were examined after treatment with female sex hormones under various conditions. The expressions of ERα, ERRα, and OPN-mRNA in whole kidney and primary cultured cells were examined using Real-Time PCR. The expressions of OPN and ERRα-mRNA were suppressed by ovariectomy. Supplementation with female sex hormones increased the expression of OPN and ERRα-mRNA. In contrast, the expression of ERα-mRNA was increased by ovariectomy and suppressed by supplementation with female sex hormones. The results of the mRNA expression in primary cultured cells matched those in the hyperoxaluric model rats. Although the reason for the difference in expression between ERα and ERRα-mRNA is unclear, estrogen may regulate OPN expression through ERα and/or ERRα, either independently or in combination. Moreover, the decrease of OPN induced by removal of estrogen may increase urinary stones in postmenopausal women.

Key words estrogen, estrogen receptor-α, estrogen receptor-related receptor-α, osteopontin, urinary stone

INTRODUCTION

Urinary stones in humans occur more commonly in adult men than adult women. Although there are some racial differences, men are affected about twice as frequently as women. However, the occurrence of urinary stones increases in women in their fifties and sixties once menopause occurs [1-3]. The lower incidence of urinary stones in premenopausal women is thought to be due to a protective effect of estrogen [4-6]. Although the exact mechanism remains unclear, this effect is thought to be similar to that of anti-arteriosclerosis [7]. On the other hand, osteopontin (OPN) is a well-known stone matrix protein, although whether it functions as an inhibitor or promoter in stone formation is unclear [8-12]. A recent report on the interaction of estrogen and OPN indicates that estrogen appears to inhibit stone formation.
formation by increasing OPN expression in the kidneys [13]. Other reports have indicated that estrogen receptor-related receptor-α (ERRα) interacts with OPN, which is closely related to estrogen receptor-α (ERα). Moreover, estrogen interacts with OPN through ERRα in osteoblast differentiation [14-16].

In the present study, we examined the interaction of ERα, ERRα and OPN-mRNA expression in a rat hyperoxaluric model. Moreover, we performed additional experiments using rat primary cultured cells. Kidney cells obtained from rats raised under various female sex hormone conditions were used to generate primary cell cultures that preserved their in vivo characteristics. The interactions of ERα, ERRα and OPN were investigated in these cultured cells after exposure to oxalate.

MATERIALS AND METHODS

Rat hyperoxaluric model

Nine-week old female Wistar rats (190 to 200g) were used in this study. Hyperoxaluric status was induced by administration of 0.5% ethyleneglycol (EG). Distilled water was given as the control. These rats were fed a standard commercial CE-2 diet. Each group consisted of 5 rats. Groups 1 and 4 consisted of normal females, Groups 2 and 5 consisted of ovariectomized females, and Groups 3 and 6 consisted of ovariectomized females receiving female sex hormone supplements, (estrogen in the form of estradiol dipropionate and progesterone in the form of hydroxyprogesterone capronate [Mochida Pharm., Tokyo, Japan]). These sex hormones were injected intramuscularly in the femoral region at 0.5 mg and 6.25 mg, respectively, once a week for three weeks. Groups 1, 2 and 3 were treated with distilled water. Groups 4, 5 and 6 were treated with 0.5% EG.

Primary cultured cells

Nine-week old female Wistar rats were divided into three groups: normal-females (A), ovariectomized-females (B) and ovariectomized-females given female sex hormone supplements under the same conditions described above (C). The rats were sacrificed after three weeks of distilled water treatment, and the kidneys were removed. Single cell suspensions were obtained by enzyme digestion (collagenase and deoxyribonuclease 1 [SIGMA chemical Co., St. Louis, USA]) and Ficoll-Hypaque solution (Pharmacia Biotech).

These cells were used to develop primary cultured kidney cells by incubation in a 25 cm² flask with 10 ml of RPMI-1640 medium supplemented with 10% fetal bovine serum (FBS). When the cultured cells were ready for study, the above media were removed and the cells were exposed to 0.5 mM potassium oxalate (KOx) or PBS (as a control) for one hour. PBS-exposed cells were divided into three groups: A (PBS), B (PBS) and C (PBS). KOx-exposed cells were also divided into three groups: A (KOx), B (KOx) and C (KOx). Experiments were performed three times.

Blood analysis

A blood sample was collected from each rat at sacrifice. Plasma calcium, creatinine and estradiol were determined (SRL Inc., Tokyo, Japan).

Urine analysis

24-hour urine was collected from each rat during the third week of the experiment, and urine volume and excretion of ionic components, including calcium, magnesium and oxalate (SRL Inc., Tokyo, Japan) were determined in each specimen. The urinary excretion of oxalate was measured under acidic conditions according to the SRL’s protocol. Blood and urine data were presented as mean ± standard deviation (SD).

Primers and probes for Real-Time PCR

Primers and probes used were from TaqMan Gene Expression Assays (Applied Biosystems, Foster City, CA, USA) as follows, Glyceraldehyde-3 phosphate dehydrogenase (GAPDH) (assay ID: Rn 99999916_s1) ; OPN (assay ID: Rn 01449972_m1) ; ERα (assay ID: Rn 00664737_m1) ; ERRα (assay ID: Rn 01479215_g1).

Reverse transcriptase for Real-Time PCR

The mRNA levels of GAPDH, OPN, ERα and ERRα in whole kidney and primary cultured cells were determined using Real-Time PCR. Total RNA was isolated from kidney and primary cultured cells using TRIZOL Reagent (invitrogen) according to the manufacturer’s protocol. Five micrograms total RNA from whole kidney and two micrograms total RNA from primary cultured cells were reverse-transcribed to cDNA. In brief, 10 μl reactions contained 5 μg or 2 μg total RNA, 1 μl of Random primers (50 ng/μl) (invitrogen), 1 μl of 10 mM dNTPs (invitrogen), and DEPC water. This mixture was incubated 10 min at 70 °C, and cooled for 2 min on ice. Next, 2 μl of 10xRT buffer (QIAGEN), 4 μl of 25 mM Mgcl 2 (QIAGEN), 2 μl of 0.1 M DTT (invitrogen), 1 μl of RNase inhibitor (Promega) and 1 μl of Super Script III (invitrogen) were added. That mixture (total 20 μl) was incubated
for 50 min at 42 °C, and again for 15 min at 70 °C.

**Real-Time quantitative PCR**

PCR products were directly monitored by TaqMan PCR assay methods (Applied Biosystems, Foster City, CA, USA). The threshold cycle (Ct) was defined as the fractional cycle number at which fluorescence exceeded the threshold level. The relative quantity of mRNA was calculated from a standard curve that used dilution methods with a reference sample. The quality of cDNA in each sample was confirmed using GAPDH as an internal reference. All PCR reactions were performed using a 7300 Real-Time PCR system (Applied Biosystems, Foster City, CA, USA). For each PCR run, the 20 μl reaction mixtures contained 10 μl of TaqMan 2X PCR Master Mix, 1 μl of TaqMan Gene Expression Assays, 8 μl of DEPC water and 1 μl of cDNA. Real-time PCR was performed according to the manufacturer’s protocol.

**Statistical analyses**

Data are presented as mean ± SD. Statistical analyses were performed by one-factor analysis of variance with a post hoc test (Fisher’s protected least-significant difference test). A result of p < 0.05 was considered to be statistically significant.

**RESULTS**

**Serum and urinary data**

Serum estradiol levels in Groups 3 and 6 were significantly higher than those in the other four groups. Moreover, the mean estradiol level of the ovariectomized groups was lower than that of the non-ovariectomized groups, although the difference was not significant. The mean serum calcium level and urinary excretion of calcium tended to be higher in the groups receiving female sex hormone (Groups 3, 6) regardless of whether the rats received distilled water or EG.

The urinary excretion of magnesium in Groups 4 and 6 was significantly higher than in Groups 1 and 2. The urinary excretion of oxalate in Group 4 was significantly higher than in Groups 1 and 6 (Table 1, 2).

**Real-Time quantitative PCR**

Figure 1 shows the relative quantities of OPN-mRNA expression. The relative quantity of OPN-mRNA was significantly lower in Group 2 (0.27 ± 0.24)

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**TABLE 1. Serum concentration of estradiol, calcium and creatinine**

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum estradiol pg/ml</td>
<td>16.2 ± 15</td>
<td>5.9 ± 2.6</td>
<td>301 ± 221.7</td>
<td>28.4 ± 17.5</td>
<td>5.7 ± 2.1</td>
<td>226.7 ± 152.8</td>
<td>&lt;0.01 Group 3 versus 1, 2, 4 and 5</td>
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<td></td>
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<td>&lt;0.01 Group 6 versus 1, 2 and 5</td>
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<td>&lt;0.05 Group 4 versus 6</td>
</tr>
<tr>
<td>Serum calcium mg/gl</td>
<td>10 ± 0.3</td>
<td>10.1 ± 0.5</td>
<td>10.5 ± 0.3</td>
<td>10.5 ± 0.3</td>
<td>10.5 ± 0.5</td>
<td>11.1 ± 1.1</td>
<td>&lt;0.05 Group 6 versus 1 and 2</td>
</tr>
<tr>
<td>Serum creatinine mg/dl</td>
<td>0.3 ± 0.1</td>
<td>0.3 ± 0.1</td>
<td>0.4 ± 0.1</td>
<td>0.3 ± 0.1</td>
<td>0.3 ± 0.1</td>
<td>0.4 ± 0.1</td>
<td>&lt;0.05 Group 6 versus 1, 2, 4 and 5</td>
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<td>&lt;0.05 Group 3 versus 4</td>
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**TABLE 2. Urinary concentration of calcium, magnesium and oxalate**

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<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary calcium mg/day</td>
<td>0.5 ± 0.2</td>
<td>0.3 ± 0.04</td>
<td>1.2 ± 0.5</td>
<td>0.5 ± 0.3</td>
<td>0.3 ± 0.1</td>
<td>1.1 ± 0.5</td>
<td>&lt;0.01 Group 6 versus 1, 2, 4 and 5</td>
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<td>&lt;0.01 Group 3 versus 1 and 5</td>
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<td>&lt;0.05 Group 3 versus 2 and 4</td>
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<tr>
<td>Urinary magnesium mg/day</td>
<td>1.1 ± 1.3</td>
<td>0.9 ± 0.6</td>
<td>2.3 ± 0.7</td>
<td>2.6 ± 2.5</td>
<td>2.5 ± 1.7</td>
<td>3.8 ± 1.5</td>
<td>&lt;0.05 Group 4 versus 1 and 2</td>
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<td>&lt;0.05 Group 6 versus 1 and 2</td>
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<tr>
<td>Urinary oxalate mg/day</td>
<td>0.2 ± 0.2</td>
<td>0.4 ± 0.3</td>
<td>0.2 ± 0.1</td>
<td>0.5 ± 0.4</td>
<td>0.4 ± 0.1</td>
<td>0.1 ± 0.03</td>
<td>&lt;0.05 Group 4 versus 1 and 6</td>
</tr>
</tbody>
</table>
than in Group 1 (0.67±0.25), and was significantly lower in Group 5 (0.5±0.22) than in Group 4 (1.1±0.75). Administration of 0.5% EG significantly boosted OPN-mRNA expression in Group 4 as compared with Group 1. In addition, the relative quantities of OPN-mRNA in Groups 3 (0.59±0.5) and 6 (0.8±0.18) were increased significantly by supplementation with female sex hormones, as compared with Groups 2 and 5. Figure 2 shows the relative quantities of ERα-mRNA expression. ERα-mRNA levels were significantly higher in the groups given 0.5% EG than in the groups given distilled water {Group 4 (0.41±0.21) versus Group 1 (0.25±0.07), Group 5 (0.6±0.27) versus Group 2 (0.34±0.31)}. Ovariectomy resulted in a significant increase in the relative quantity of ERα-mRNA in Group 5 as compared with Group 4. In contrast, supplementation with female sex hormones produced a significant decrease in the relative quantity of ERα-mRNA in Group 3 (0.14±0.06) as compared with Group 2, and in Group 6 (0.17±0.05) than in Group 1 (0.67±0.25), and was significantly lower in Group 5 (0.5±0.22) than in Group 4 (1.1±0.75). Administration of 0.5% EG significantly boosted OPN-mRNA expression in Group 4 as compared with Group 1. In addition, the relative quantities of OPN-mRNA in Groups 3 (0.59±0.5) and 6 (0.8±0.18) were increased significantly by supplementation with female sex hormones, as compared with Groups 2 and 5. Figure 2 shows the relative quantities of ERα-mRNA expression. ERα-mRNA levels were significantly higher in the groups given 0.5% EG than in the groups given distilled water {Group 4 (0.41±0.21) versus Group 1 (0.25±0.07), Group 5 (0.6±0.27) versus Group 2 (0.34±0.31)}. Ovariectomy resulted in a significant increase in the relative quantity of ERα-mRNA in Group 5 as compared with Group 4. In contrast, supplementation with female sex hormones produced a significant decrease in the relative quantity of ERα-mRNA in Group 3 (0.14±0.06) as compared with Group 2, and in Group 6 (0.17±0.05)
as compared with Group 2.

Figure 3 shows the relative quantities of ERRα-mRNA expression. ERRα-mRNA levels were significantly lower in ovariectomized Group 2 (0.18 ± 0.12) than in Group 1 (0.34 ± 0.06), and were also significantly lower in ovariectomized Group 5 (0.25 ± 0.09) than in Group 4 (0.42 ± 0.09). Administration of 0.5% EG significantly boosted ERRα-mRNA expression in Group 4 as compared with Group 1. In addition, the relative quantity of ERRα-mRNA in Group 3 (0.34 ± 0.1) was increased significantly by supplementation with female sex hormones, as compared with Group 2. The changes in OPN-mRNA expression resembled those in ERRα-mRNA expression. However, the changes in ERα-mRNA expression were negatively correlated with those of OPN and ERRα-mRNA.

Figure 4 shows the relative quantities of OPN-mRNA expression in primary cultured cells. In the KOx exposed cells, ovariectomy resulted in a significant decrease in the relative quantity of OPN-mRNA expression. The expression of OPN-mRNA in Group (KOx) (0.52 ± 0.17) was significantly lower than in Group (KOx) (1.14 ± 0.13). The expression of OPN-mRNA was significantly higher in Group (KOx) and C (KOx) (1.06 ± 0.32), which were exposed to KOx, than in Group (PBS) (0.61 ± 0.25) and C (PBS) (0.45 ± 0.2). The expression of OPN-mRNA was significantly higher in C (KOx), which received female hormone supplements, than in Group (KOx).

Figure 5 shows the relative quantities of ERα-mRNA expression in primary cultured cells. The relative quantities of ERα-mRNA expression in each group were: A (PBS): (0.3 ± 0.13); B (PBS): (0.38 ± 0.12); C (PBS): (0.26 ± 0.09); A (KOx): (0.36 ± 0.1); B (KOx): (0.53 ± 0.28); and C (KOx): (0.41 ± 0.37). The changes in mean relative quantities of ERα-mRNA expression, although not statistically significant, resembled those of the ERα-mRNA expression in the rat hyperoxaluric model. In addition, the mean relative quantities of ERα-mRNA were increased by exposure to KOx.

Figure 6 shows the relative quantities of ERRα-mRNA expression in primary cultured cells. The relative quantities of ERRα-mRNA expression in each group were: A (PBS): (0.81 ± 0.49); B (PBS): (0.66 ± 0.23); C (PBS): (0.74 ± 0.21); A (KOx): (1.0 ± 0.18); B (KOx): (0.99 ± 0.12); and C (KOx): (1.1 ± 0.54). The changes in mean relative quantities of ERRα-mRNA expression in primary cultured cells, although not statistically significant, resembled those of the ERRα-mRNA expression rat hyperoxaluric model.
in Group B (KOx) (0.52±0.17) as compared with Group A (KOx) (1.14±0.13). In contrast, supplementation with female sex hormones produced a significant increase in the relative quantity of OPN-mRNA in Group C (KOx) (1.06±0.32) as compared with Group B (KOx). OPN-mRNA expression was boosted significantly by exposure to KOx in Group A (KOx) as compared with Group A (PBS) (0.61±0.25), and in Group C (KOx) versus Group C (PBS) (0.45±0.2).

Figure 5 shows the relative quantities of ERα-mRNA expression in primary cultured cells. The changes in mean relative quantities of ERα-mRNA expression although not significant, were similar to the changes in ERα-mRNA expression in the rat hyperoxaluric model.

Figure 6 shows the relative quantities of ERRα-mRNA expression in primary cultured cells. As was the case with ERα, the changes in mean relative quantities of ERRα-mRNA expression in the primary cultured cells resembled those of ERα-mRNA expression in the rat hyperoxaluric model.

**DISCUSSION**

Calcium oxalate (CaOx) stones are the most common type of urinary stone in humans, and their occurrence has been increasing in recent years. Although formation of upper urinary tract CaOx stones is related to lifestyle and dietary habits, the mechanism underlying the formation of these stones remains unclear. However, upper tract urinary stones occur more commonly in men than women by a ratio of about 2:1 [1-3]. In women, however, the occurrence of CaOx stones increases after menopause and peaks in the fifth to sixth decades of life. From these findings, it has been suggested that women are protected against stone formation by the effect of estrogen in the premenopausal state. Indeed, according to recent reports, urinary excretion of calcium, oxalate and uric acid was lower in women than men. Moreover, compared with men, urinary calcium was lower in women until the age of 50 years, when it equaled that of men [4]. Citrate was equal in both genders until the age of 60 after which it tended to decrease in women [17]. On the other hand, surgical menopause is associated with an increased risk of stone formation. The sudden loss of ovarian production of estrogens and androgens in women with surgical menopause leads to a more rapid bone loss compared with women experiencing natural menopause [5,6].

In the present study, the mean urinary excretion of calcium was lower in the ovariectomized Groups 2 and 5 than in the non-ovariectomized Groups 1 and 4, although the differences were not significant. Moreover, the addition of female sex hormones was found to increase calcium excretion. Although these findings differ from those of previous reports on human urinary stones, they are partially compatible with findings in studies of postmenopausal women and in rat urinary stone models [13,18,19]. It is unclear why urinary calcium excretion was increased by supplementation with female sex hormones. The supplementary dose of female sex hormones in this study was approximately five times the normal level in human females, so over supplementation of female sex hormones may have induced increased calcium absorption in the gut [17]. Moreover, these reports indicated that higher urinary calcium excretion due to estrogen supplementation did not increase the risk of calcium renal stone formation. In addition, animal studies have shown that decreases in estrogen affect urinary oxalate levels. In ovariectomized rats, the administration of estrogen has been shown to decrease urinary oxalate excretion by over 50% [18]. In the present study, urinary excretion of oxalate decreased significantly in Group 6 as compared with Group 4.

On the other hand, as regards the interaction between sex hormones and stone matrix protein, estrogen appears to inhibit stone formation by increasing OPN expression in the kidneys [13]. Although OPN is a well-known stone matrix protein, whether it functions as an inhibitor or promoter in stone formation is unclear. Some reports, suggest that OPN protects renal epithelial cells from anti CaOx crystal injury [8-10]. But other reports have shown that CaOx attachment was inhibited in OPN antisense transfected renal epithelial cells [11,12].

However, ERα in the kidney regulates estrogen, which may protect against renal epithelial cell damage. Estrogen similarly protects against epithelial cell damage in arteries. The interaction of estrogen and OPN in urinary stone formation is probably similar in mechanism to that of arteriosclerosis or aortic calcification [7].

In addition, ERRα is an orphan nuclear receptor that regulates the OPN gene, and ERRα is closely related to ERα. ERRα is expressed in a variety of adult and embryonic tissues, and interacts with OPN in osteoblast differentiation [14-16].

In our study, the expressions of OPN and ERRα-mRNA were decreased significantly in ovariectomized rats (Groups 2 and 5) as compared with non-ovariectomized rats (Groups 1 and 4), regardless of whether they were administered distilled water or 0.5% EG.
Further, these expressions were increased by supplementation with female sex hormones (Groups 3 and 6). Thus, there is a possibility that OPN and ERRα-mRNA expression were controlled by estrogen. Previous reports have shown that although estrogen is not an ERRα-ligand, it stimulates ERRα expression in uterus or breast tissue [20-22]. Moreover, the expression of OPN and ERRα-mRNA in groups receiving 0.5% EG tended to be higher than in the groups given distilled water, and the changes in OPN-mRNA were similar to those in ERRα-mRNA expression. These findings indicate a possibility that ERRα expression stimulated ERα target genes in the absence of estrogen. Previous reports have in fact shown that ERRα can stimulate ERα target genes in the absence of estrogen. In addition, over expression of ERRα can stimulate ERE (estrogen-responsive element) dependent transcription in ER-negative cells [20,23].

On the other hand, in our study, ERα-mRNA expression was increased by ovariectomy, despite a decrease in OPN and ERRα-mRNA expression. Moreover, supplementation with female sex hormones produced a significant decrease in the expression of ERα-mRNA. Although more investigation is necessary to explain these results, similar findings were reported previously. According to these reports, ER positivity was significantly higher in the subepithelial tissues of the vagina in postmenopausal women not receiving hormone replacement therapy than in either premenopausal women or women receiving estrogen supplementation. Similar results were seen in rats [24,25].

Moreover, it was reported that ovariectomy upregulates expression of ERs in porcine platelets [26]. Therefore, there are currently two different models of the relationship between estrogen and ER signaling. In model-1, estrogen exposure causes a rapid down-regulation of ER-mRNA and protein, and up-regulation in the absence of estrogen. In this model, the primary response to an estrogenic stimulus is a feedback inhibition of ER-mRNA levels. Conversely, in model-2, estrogen exposure causes an increase in the ER-mRNA level and protein [27]. ER expression in renal epithelial cells, which maintain rapid cell proliferation to prevent cell injury, may be regulated by a mechanism of this model-1.

Moreover, a study of ER-levels in MCF-7 human breast cancer cells grown in short-term or long-term absence of estrogens reported that while cells grown in the short-term absence of estrogens have ER-levels similar to those of control cells, cells grown in the long-term absence of estrogens have ER-levels three times higher than controls. In addition, these latter cells maintained high sensitivity to estrogen despite a long-term absence of estrogen [28]. These findings suggest that high levels of expression and sensitivity are maintained in renal epithelial cells despite a long-term absence of estrogen.

Although we examined the interaction of estrogen and OPN through ERα and ERRα expression, the findings of the present study do not necessarily apply to human urinary stones. Moreover, in rat hyperoxaluric models, results differ depending on the conditions of stone formation [29]. As a result, the present investigation of changes in female sex hormone receptors in such unusual states may not produce meaningful results.

Therefore, we carried out another experiment using primary cultured cells developed from kidney cells of rats raised under various female sex hormone conditions. Our results showed that the changes of OPN, ERα, and ERRα-mRNA expression after exposure to PBS or KOx were similar to those in the rat hyperoxaluric model.

In summary, though it is unclear whether ERRα or ERα function independently or together in regulation of target genes in various cells, it is apparent that ERRα modulates the ERα mediated signaling pathway both positively and negatively [21,23,30]. On the other hand, ERα can stimulate ERα target genes in the absence of estrogen. In the interaction of ERα, ERRα and OPN, ERRα is a direct target of ERα activity, and ERRα induces ERα expression in the breast. Moreover, ERα stimulates the estrogen-responsive gene, OPN [20]. Our current findings are in agreement with the above reports.

Although it is unclear why there was a negative correlation between ERα and ERRα-mRNA expression in the present study, estrogen may regulates OPN expression through ERα or ERRα or both in combination. Moreover, the decrease of OPN induced by removal of estrogen may increase the incidence of urinary stones in postmenopausal women.

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INTRODUCTION

Although the initial success of cardiopulmonary resuscitation (CPR) is quite high, the majority of victims die within several days. The main cause of circulatory collapse following CPR is considered to be myocardial dysfunction [1]. Therefore, careful and quick management of deteriorated myocardium is essential in post-resuscitation cases. This report describes the anesthetic management of a patient with low cardiac function after CPR, who underwent emergent aortic replacement for the ruptured AAA.

Summary: A 73-year-old woman suffering from an abdominal aortic aneurysm (AAA), unstable angina, and low cardiac function (32% of ejection fraction) was scheduled for abdominal aortic replacement and coronary artery bypass grafting. However, before the scheduled operation the patient fell into cardiopulmonary arrest with ventricular fibrillation due to rupture of the AAA. Immediate cardiopulmonary resuscitation (CPR) using epinephrine and electrical defibrillation restored the spontaneous circulation. Following CPR, a continuous high-dose dopamine infusion (15 μg/kg/min) was initiated and emergent abdominal aortic replacement was performed. On arrival at the operating room, the patient showed serious hypotension, atrial fibrillation with multifocal ventricular premature contractions, and metabolic acidosis. Transesophageal echocardiography (TEE) suggested that the circulatory collapse might have resulted from diastolic dysfunction and deteriorated compliance of the left ventricular (LV) wall, possibly due to myocardial stunning induced by myocardial ischemia, and tachycardia induced by hypovolemia, both of which are influenced by high doses of catecholamine. We accordingly transfused adequate amounts of blood products and gradually decreased the infusion rate of dopamine to 4 μg/kg/min, while carefully monitoring blood pressure, central venous pressure, and TEE. By the end of surgery hemodynamic parameters had recovered to near normal levels. In post-resuscitated and hypovolemic patients, caution should be taken when administering high levels of exogenous catecholamines, which can induce myocardial stunning and circulatory collapse.

Key words cardiopulmonary resuscitation, catecholamine-induced myocardial stunning, diastolic dysfunction, transesophageal echocardiogram
CASE REPORT

A 73-year-old woman (height, 151 cm; weight, 55 kg) suffering from an AAA (diameter 8.4 cm) and unstable angina was scheduled for abdominal aortic replacement and coronary artery bypass grafting (CABG). Preoperative examinations showed coronary artery stenosis (right coronary artery, 90%; circumflex artery, 100%; left anterior descending artery, 90%), aortic root diameter; 37 mm, left atrial dimension; 45 mm, interventricular septum thickness; 12 mm, posterior left ventricular (LV) wall thickness; 9 mm, LV end-diastolic dimension; 55 mm, LV end-systolic dimension; 47 mm, fractional shortening; 14.5%, an ejection fraction (EF) of 32% and severe hypokinesis in the posterior to inferior myocardial wall motion.

Twenty days before the scheduled operation, the patient had sudden abdominal pain, which resulted in cardiopulmonary arrest (CPA) with ventricular fibrillation (VF) due to rupture of the AAA. Immediate CPR using a total amount of 2 mg of intravenous epinephrine and electrical defibrillation with endotracheal intubation resulted in the restoration of spontaneous circulation (ROSC). Approximately 45 min after the ROSC, emergent surgery to repair the ruptured AAA was performed. On arrival at the operating room, a continuous infusion of high-dose dopamine (15 μg/kg/min) was started. The patient showed hypotension (systolic blood pressure: SBP, 50 mmHg), tachycardia (heart rate: HR, 128 bpm) with atrial fibrillation (AF), and multifocal ventricular premature contraction (VPC). Analysis of arterial blood revealed metabolic acidosis (FIO₂, 1.0; pH, 7.14; PaO₂, 541 torr; PaCO₂, 35 torr; HCO₃⁻, 11.4 mmol/l; base excess (BE), –16.5 mmol/l) and 451 mg/dl of glucose.

Tracheal intubation had already been performed, and anesthesia was induced with 7.5 mg of midazolam and maintained with a gas mixture of oxygen, air, and 1% sevoflurane, in combination with continuous nicorandil and intermittent fentanyl and rocuronium as needed. The monitoring included electrocardiogram (ECG), SpO₂, P₉₅CO₂, left radial arterial blood pressure (ABP), central venous pressure (CVP) via a catheter placed through the right internal jugular vein, and transesophageal echocardiography (TEE). The initial monitoring showed serious hypotension (SBP<50 mmHg), tachycardia with AF and VPCs, and elevated CVP (>18 mmHg); TEE indicated that both atria were dilated, with a reduction in LV chamber size and an increase in wall thickness; the EF was calculated to be.

![Graph](image-url)  

**Fig. 1.** Changes in hemodynamic parameters (SBP, DBP, HR and CVP) and doses of the anesthetics (sevoflurane and fentanyl), insulin, cardiovascular agents (nicorandil and dopamine) and blood transfusion products.
of circulatory collapse in the post-resuscitation period even after initially successful ROSC. The major cause of these conditions could have resulted from myocardial stunning induced by myocardial ischemia and tachycardia induced by hypovolemia; both conditions can be influenced by high doses of catecholamine. Based on these suppositions, the infusion rate of dopamine was decreased by degrees, and an adequate amount of blood products was transfused continuously under the careful monitoring of SBP, CVP, and TEE throughout the surgery (Fig. 1). The following blood products were transfused during the surgery against intraoperative 10,420 g of blood loss and 265 ml of urine output: 34 units of packed red blood cells, 28 units of fresh frozen plasma, 20 units of concentrated platelets, and 1,750 ml of crystalloidal or colloidal solutions. Consequently, SBP, HR, and CVP were steadily restored to normal limits, with TEE showing better LV contraction along with sufficient diastolic function. The ruptured AAA was uneventfully replaced just below the bilateral renal arteries and above the bifurcation of the common iliac artery in 295 min. At the end of surgery, ABP, HR, CVP, EF, and cardiac output were 95/48 mmHg, 66 bpm, 10 mmHg, 38%, and 2.8 l/min, respectively, with the use of dopamine at an infusion rate of 4 μg/kg/min. The values of arterial blood analysis were as follows: pH 7.40, PaO2 323 torr, PaCO2 35 torr, HCO3⁻ 21.5 mmol/l, BE – 2.3 mmol/l in FIO2 of 0.6, Hb 10.2 g/dl, and glucose 154 mg/dl using a continuous venous insulin infusion. No ischemic change was observed and VPCs were almost completely absent on ECG throughout the procedure.

The patient was transferred to the intensive care unit, where mechanical ventilation was continued under sedation with propofol for 2 days, and the trachea was extubated on postoperative day (POD) 3 without any complications, including neurological deficits. However, difficulties in the management of unstable angina made it necessary for her to undergo CABG on POD 7, after which she made a remarkable recovery except for a minor surgical site infection.

DISCUSSION

Following CPR, many patients experience hemodynamic instability and can easily develop circulatory collapse, including hypotension, ventricular arrhythmias, and recurrent CPA, which can lead to early death even after initially successful ROSC. The major cause of circulatory collapse in the post-resuscitation period is considered to be myocardial stunning [1]. Our patient developed CPA because of myocardial ischemia following severe hypotension and ruptured AAA. ROSC was achieved by advanced cardiac life support involving the administration of epinephrine and electrical defibrillation, followed by a continuous infusion of high-dose dopamine. However, the patient fell into circulatory collapse after ROSC, probably due to diastolic dysfunction and deteriorated compliance of the LV wall. These LV conditions may have resulted from myocardial stunning induced by myocardial ischemia and administration of epinephrine during CPR accompanied by high doses of dopamine. The deteriorated diastolic dysfunction was deemed to be associated with rapid AF (induced by hypovolemia and high doses of catecholamine), and previous myocardial infarction. On the basis of SBP, HR, CVP, and TEE data, our priority was to restore hemodynamic function by improving LV wall compliance and increasing LV end-diastolic volume. We gradually decreased the infusion rate of dopamine while transfusing an adequate amount of blood products, which resulted in an improvement in cardiac dysfunction and hemodynamics.

Catecholamines are often given continuously during the post-resuscitation period in order to maintain hemodynamic stability. On the other hand, catecholamine-induced myocardial stunning can be caused by a surge in blood concentrations of catecholamines in association with the induction of β-adrenoreceptor (β-AR). Catecholamines such as epinephrine, dopamine and dobutamine, especially in high doses, may increase myocardial oxygen consumption, resulting in an imbalance between myocardial oxygen supply and demand, which can produce myocardial stunning [2-8]. In our case, continuous infusion of high-dose dopamine had been initiated immediately following epinephrine administration for CPR, suggesting that these catecholamines might have exacerbated cardiac dysfunction in the post-resuscitation period. The effects of surged catecholamine levels on myocardial stunning and the induction of β-AR are reversible after catecholamine levels return to normal [8,9]. Some investigators have reported that blockade of β-AR significantly improves the initial outcomes of CPR, minimizes post-resuscitation myocardial dysfunction, and increases the duration of survival [7,10-12]. Although no β-AR blocking agents were administered in our case, stable cardiac function was obtained by reducing the infusion rate of dopamine while transfusing adequate volumes of blood products. Our present results suggest that excessive doses of catecholamine, as a β-AR agonist, induce myocardial stunning.
Acidosis may impair cardiac resuscibility and reduce the myocardial response to catecholamines [13]. Acidosis should therefore be corrected to improve success in CPR and to allow for a reduction in the dose of catecholamines administered. In any case, the careful and speedy management of deteriorated myocardium is essential for patients after CPR, and appropriate monitoring of hemodynamics is of great importance in this regard. TEE may be very suggestive and is widely used to evaluate cardiac function, as shown in our case. This case report does have limitations. Although diastolic function is typically evaluated by means of transmitral valve blood flow (TMF) velocity, pulmonary venous blood flow (PVF) velocity, and tissue Doppler imaging (TDI), its evaluation by means of TMF and PVF in patients with AF is difficult. It is even more difficult to evaluate diastolic function in a critical situation, such as the case presented here. As a result, we are unable to present objective data, such as echocardiography, to demonstrate that high doses of dopamine suppressed diastolic function.

In summary, we have described the anesthetic management of a patient with CPA due to ruptured AAA and cardiac dysfunction following CPR. In post-resuscitation patients, particular attention should be paid to high levels of exogenous catecholamines, which can induce myocardial stunning and circulatory collapse.

REFERENCES
A Case of Acute Disseminated Encephalomyelitis Mimicking Leukodystrophy

AVNI KAYA, MEHMET ACIKGOZ*, LOKMAN USTYOL*, SERHAT AVCU**, ERTAN SAL*, MESUT OKUR AND HUSEYIN CAKSEN*

Department of Pediatrics, Women and Children’s Hospital, Departments of Pediatrics* and Radiology**, Yüzüncü Yıl University, Van 65100, Turkey

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Summary: Acute disseminated encephalomyelitis (ADEM) is a monophasic, immune-mediated demyelinating disorder that can follow immunizations or more often infections including rubeola, rubella, varicella, herpes zoster, mumps, Mycoplasma pneumoniae, or, more commonly, other nonspecific upper respiratory tract infections. Documentation of a preceding illness is not required to make this diagnosis. This report examines the case of a 9-month-old male patient presenting with the features of an acute leukodystrophy following inoculation with the mixed vaccine Pentaxim (Sanofi Pasteur, Lyon-France) while suffering from a lower respiratory tract infection, and who was eventually diagnosed as ADEM. The case is presented as a reminder that ADEM can sometimes be linked to lower respiratory tract infection and vaccination, and that the features in such cases can be confused with leukodystrophy.

Key words vaccination, demyelinating, leukodystrophy

INTRODUCTION

Acute disseminated encephalomyelitis (ADEM) is a monophasic, immune-mediated demyelinating disorder that can follow immunizations or more often infections including rubeola, rubella, varicella, herpes zoster, mumps, Mycoplasma pneumoniae, or, more commonly, other nonspecific upper respiratory tract infections. Documentation of a preceding illness is not required to make this diagnosis [1]. The present case was pathologically characterized by perivascular inflammation, edema and demyelination. Clinically, this disease can be restricted to systemic features and observations that are not specific to it, or fast evolving focal or multifocal neurological function deficiencies can be observed [2]. In this report, the case of a 9-month-old male patient presenting with the features of an acute leukodystrophy following treatment with the mixed vaccine Pentaxim (Sanofi Pasteur, Lyon-France) while suffering from a lower respiratory tract infection, and eventually diagnosed as ADEM is examined.

CASE PRESENTATION

A 9-month-old male patient was hospitalized after suffering a seizure during a fever. Patient history revealed repeating episodes of fever and dry cough in the two weeks prior to admission. Cefixime and ibuprofen treatment had been started after a diagnosis of bronchitis at a local health center. During a period of fever experienced two hours before admission, the patient suffered three five-minute long generalized tonic-clonic type convulsions. This patient, who did not have any insect sting antecedents, had been vaccinated with mixed Pentaxim vaccine five days earlier. A cyst in the...
cerebral choroid plexus had been identified by intrauterine ultrasonography. The patient’s father had a history of posttraumatic epilepsy from which he had recovered.

At physical examination, the general condition of the patient was mean and he exhibited postictal awareness. The body temperature was 39°C. The maximal heart rate was 142/minute and his arterial tension was 100/70 mmHg. The pupillary isochoric, direct and indirect light reflexes were obtained. His deep tendon reflexes were regular. The patient weighed 10.4 kg (75-90 percentile), and his height was 73 cm (75-90 percentile). The frontal fontanella was 2×2 cm and at a normal cambering level. Crepitant rales were present on the right side at some locations in the respiratory system.

Laboratory examinations revealed a leukocyte count of 13,840/mm³, a hemoglobin value of 10.4 g/dL, and a thrombocyte count of 451,000/mm³. Prothrombin time and activated partial thromboplastin time were normal. The blood gas values were within normal limits. The C-reactive protein was 3 mg/L and the sedi-

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**Fig. 1.** Brain magnetic resonance imaging made during the eighth month (Axial T2-weighted image).

**Fig. 2.** Diffuse decrease of the white matter density in the emergency brain computed tomography.

**Fig. 3.** A large signal increase in the white matter, especially on axial (a) and sagittal (b) T2 series was obtained.
mentation was 30 mm/h. Liver and renal function, vitamin B₁₂, folate hormone and thyroid hormone levels were also normal. The cerebrospinal fluid (CSF) obtained by lumbar puncture did not contain any cells by direct observation. The glucose and protein levels of the CSF were normal. The results of electroencephalogram were within normal range. Metabolic screening tests performed by tandem MASS spectrometer were negative.

The patient was admitted because of pneumonia and febrile convulsions. Intravenous penicillin and chloramphenicol treatment was started. A cyst in the cerebral choroid plexus had been identified in the intrauterine ultrasonography. A brain magnetic resonance imaging (MRI) obtained during the eighth month was used to manage this cyst (Fig. 1). The three seizures of the patient and the observation of a diffuse decrease of the white matter density in the emergency computed tomography of the brain (Fig. 2) led to the observation of a large signal increase in the white matter of the two cerebral hemispheres, especially on T₂ series by MRI (Fig. 3).

The disappearance of symptoms on the tenth day of monitoring allowed the discharge of the patient with a single antiepileptic (phenobarbital). The large extent of the involvement on brain MRI led to the diagnosis of Cree leukodystrophy. That is why no steroid treatment was given. On follow-up, the brain MRI results obtained at 45 days after admission were normal, so the diagnosis of Cree leukodystrophy was rejected and a diagnosis of ADEM was proposed. The patient was then considered as having experienced a lower respiratory tract infection followed by ADEM (Fig. 4).

**DISCUSSION**

The onset of Cree leukoencephalopathy is between 3 and 9 months of age with 100% mortality by 21 months of age. Hypotonia is often noted in early infancy followed by a relatively sudden onset of seizures, spasticity, hyperventilation, vomiting, and diarrhea, often in the setting of a febrile illness. Onset is followed by developmental regression, lethargy, blindness, and cessation of head growth seen as flattening of the head circumference curve [3]. Computerized tomography of the head shows symmetrically hypodense white matter. Similar images were obtained on T₁-weighted head MRI that showed symmetrical diffuse attenuation of hemispherical and often cerebellar white matter [4]. T₂-weighted MRI showed hyperintense white matter that included the subcortical fibers, basal ganglia, and thalamus. Microscopic examination showed diffuse white matter vacuolation in some cases and astrogliosis with presence of oligodendrocytes and cells described as lipid-laden macrophages [3,4].

In countries where vaccination coverage is inadequate, the most recurrent causes of ADEM are measles, mumps, rubella, and varicella, while in other countries nonspecific upper respiratory infection and coronavirus can constitute a factor. Almost half of the
patients are older than five years [5]. Around 0 to 12% of the cases with ADEM report a vaccination episode before the attack [6].

Pentaxim contains diphtheria toxoid, Tetanos toxoid, the antigens of Bordetella pertussis, the inactivated poliovirus and the type b polysaccharide of Hemophilus influenzae. Routine vaccination with Pentaxim started in Turkey at the beginning of 2008.

The levels of CSF constituents are normal in 25 to 75% of the patients with ADEM. An increased CSF pressure, a lymphocytic pleiocytose (up to 1000/mm³; 75% of the patients with ADEM. An increased CSF activated polyomyelitis virus and the type b polysaccharide of Hemophilus influenzae. Routine vaccination with Pentaxim started in Turkey at the beginning of 2008.

The levels of CSF constituents are normal in 25 to 75% of the patients with ADEM. An increased CSF pressure, a lymphocytic pleiocytose (up to 1000/mm³; sometimes polymorph leukocytes are preponderant in the beginning period) and an increase of protein level can be determined [5]. In our patient, there were no CSF cells and his biochemistry was normal. The diagnosis of ADEM can be established using clinical and cerebral MRI. The lesions observed by MRI are usually large and asymmetrical, and tend to be numerous and always present with bilateral localization. The distribution of the lesions can be quite variable. The most commonly observed localizations are the corticomedullar section, the corpus callosum, the medial cerebellar stem, the cerebellum, the brain stem and basal ganglia, but ar especially noted in the semioval central and corona radiata white matter [7].

Three MRI examinations were performed in the present case. The first took place after the identification of a cerebral choroid plexus cyst by intrauterine ultrasonography. This MRI showed a bifrontal enlargement combined with benign subarachnoidal distance increase and mega cisterna magna. The emergency brain computed tomography performed after the patient’s three seizures led to the observation of a diffuse decrease in white matter density, which was the reason for the second MRI examination. It has been suggested that MRI could be useful in the diagnosis of ADEM. The third MRI examination was performed 45 days after the hospitalization as a control, and the results were normal. So the final diagnosis was made of lower respiratory tract infection and ADEM linked to Pentaxim vaccine. ADEM cases linked to vaccines have been reported in Turkey [8] and abroad [9,10], however, this is the first case in which an ADEM appeared after lower respiratory tract infection and inoculation with Pentaxim vaccine.

In more than 70% of ADEM cases, healing occurs in the first 6 months [5]. Some neurological traces remain at different levels in 11 to 30% of the patients. The sequelae proportion is higher in patients presenting large or bilateral thalamus lesions [5]. Although the mortality rate can reach 10 to 20%, most patients experience a complete recovery [11].

Most ADEM lesions are asymmetrical, but rapidly developing and symmetrical ones have also been reported. According to Nishimura et al, [12] “MRI showed extensive symmetric high signal lesions in the bilateral cerebellar and cerebral white matters.” Imamura and Sakai [13] reported a case of early-onset acute disseminated encephalomyelitis in which “MRI showed extensive symmetric high signal lesions in bilateral cerebral white matters which were demonstrable in the sagittal image.” Kawashima et al. [14] reported in two cases “fluid attenuated inversion recovery (FLAIR) sequenced MRI showed multiple symmetric hyperintense lesions in the internal capsule and the brainstem at the subacute stage.”

Although the presence of lesions suggested reversible posterior leukoencephalopathy syndrome (RPLS), fever and associated convulsion was observed in our patient. In RPLS, convulsions can be observed without fever. Our patient was mildly hypertensive, but this condition was transient, and there was no need to use antihypertensive medication. On the other hand, serious hypertension is expected in RPLS [15]. The lesions are located posteriorly in RPLS [15], whereas there was widespread involvement in our case.

Patients diagnosed with ADEM are treated for 3 to 5 days with a high dose of intravenous methylprednisolone (20-30 mg/kg/day). Depending on the pace of regression of the clinical features, treatment with oral prednisolone at a dose of 2 mg/kg/day can be started and a decreasing dose can be administrated for 4 to 6 weeks [16]. If the treatment is not adequate, plasmapheresis or intravenous immunoglobulines constitute an alternative treatment [17]. However, Cree leukoencephalopathy was the initial diagnosis in our patient and he was followed-up accordingly. After the disappearance of the lesions present in the brain, a diagnosis of ADEM was accepted. That is why no treatment was given. Our patient healed spontaneously without treatment.

CONCLUSION

The present case may serve as a useful reminder that it is possible to observe ADEM linked to lower respiratory tract infection and vaccination, and that the features of such cases can be confused with leukodystrophy.

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