Extrapontine Myelinolysis in a Patient with Primary Adrenal Insufficiency

Jr-Wei Wu[1], Pei-Ning Wang[1,3], Jiing-Feng Lirng[2,3], Ruei-Wen Hsu[1], Wei-Ta Chen[1,3]

Abstract

Purpose: To report the development of extrapontine myelinolysis (EPM) in a patient with adrenal insufficiency and review similar cases in the literature.

Case Report: A 49-year-old female with adrenal insufficiency presented with acute dysarthria, stuttering, and parkinsonism. She received isotonic saline hydration for adrenal crisis and hyponatremia 18 days before the onset of symptoms. The brain MRI and MRS showed demyelination at bilateral basal ganglia and the thalamus, which was compatible with EPM and resolved within 3 months after steroid treatment.

Conclusion: Development of acute parkinsonism after rapid correction of hyponatremia may indicate the occurrence of EPM and underlying adrenal insufficiency should be excluded in these patients.

Key Words: osmotic demyelinating syndrome, extrapontine myelinolysis, adrenal insufficiency, hyponatremia

Acta Neurol Taiwan 2014;23:146-152

INTRODUCTION

Central pontine myelinolysis (CPM) is a severe, life-threatening neurological condition that is characterized by demyelination in the basis pontis, sparing the tegmentum. CPM was first described in 1959 and was linked to alcoholism and malnourishment initially [(1)]. Later, rapid correction of hyponatremia was regarded as the main culprit [(2)]. A similar syndrome with demyelinating lesions outside of the pons was first reported in 1962, and named "extrapontine myelonolysis". We now use the collective term osmotic demyelination syndrome (ODS) to refer to myelinolysis involving centropontine or extrapontine regions or both [(4)].

Isolated EPM without CPM is relatively rare. In a study of 58 patients with ODS [(3)], 27(45%) were pure CPM, 13(22.4%) were pure EPM and the remaining 18 (31%) were combined CPM with EPM. Isolated EPM without CPM accounted for 20% of all ODS cases in another study[(4)]. Herein, we report a patient with adrenal insufficiency that had developed acute parkinsonism at presentation. Without the initial history of hyponatremia and rapid sodium replacement, the final diagnosis of EPM was delayed until confirmation by brain magnetic

From the [1]Neurological Institute, [2]Department of Radiology, Taipei Veterans General Hospital, Taipei, Taiwan, [3]School of Medicine, National Yang-Ming University, Taipei, Taiwan.
Received November 1, 2013. Revised November 15, 2013. Accepted April 8, 2014.
Correspondence to: Wei-Ta Chen, MD, Ph.D. Neurological Institute, Taipei Veterans General Hospital, 201, Shihpai Rd Sec 2, Taipei, 112 Taiwan (ROC)
E-mail: wtchen@vghtpe.gov.tw

resonance imaging (MRI) and spectrometry (MRS). The diagnostic pitfalls of EPM are discussed. Based on a literature review, we also propose a possible link between adrenal insufficiency and EPM.

CASE PRESENTATION

A 49-year-old female was admitted to Taipei Veterans General Hospital in March 2013 due to acute dysarthria and stuttering noted for 10 days. Besides adrenal insufficiency and thyroid multinodular goiter, she denied any systemic or neurological disease. She had been taking an oral steroid supplement with prednisolone 5 mg every other day for 3 years.

On Feb 13, 2013, she was hospitalized in a local hospital because of herpes zoster at the right T4 dermatome. She discontinued steroid on the day of admission and received intravenous acyclovir. Two weeks later, she was discharged in a stable condition. However, acute general weakness and irritability developed the day after discharge (Feb 26, 2013, referred to as Day 1). She was taken to another local hospital and told she had hyponatremia (113 mmol/L). After normal saline hydration with 1000 mL/day and steroid re-introduction (intravenous hydrocortisone 100 mg Q12H), she regained full muscle power and other neurological functions, and was discharged on Day 15 with oral prednisolone 5 mg daily. However, on Day 19, she developed progressive dysarthria and stuttering, so she was admitted to Taipei Veterans General Hospital on Day 29.

Neurological examinations revealed her speech was monotonous, reduced in loudness and impaired in fluency. She also had mild rigidity of the right limbs and generalized hyporeflexia. Consciousness, cranial nerve functions, muscle strength, coordination and sensation were all intact. Laboratory investigations revealed no abnormality in the complete blood count, biochemistry, electrolyte status, thyroid function, tumor markers, and autoimmune profiles. The ACTH stimulation test confirmed her primary adrenal insufficiency.

The brain MRI at admission (Figure 1) revealed small T2 hyperintensities at the bilateral thalamus. Ischemic stroke was not likely because the lesion localization seemed incompatible with specific vascular territory. Moreover, hepatic and renal functions and serum glucose were all normal. A scalp electroencephalography revealed intermittent slowing at the bilateral frontotemporal regions, but no periodic discharges typical of Creutzfeldt-Jakob disease. A brain CT absent basal ganglia calcification excluded Fahr Disease. Analysis of cerebrospinal fluid showed normal cytology, cell counts (white cell count: 4/cumm; red cell count: 240/cumm; protein 34 mg/dL; glucose 64 mg/dL) and negative culture studies for viruses, bacteria and tuberculosis. Ceruloplasmin was slightly decreased (at 20.3 mg/dL) and 24-hour urine copper was normal (at 25 ug); there were no Kayser-Fleischer rings.

A retrospective review of her medical records before admission to our hospital revealed a history of fast correction of hyponatremia (from 113.0 to 127.0 mmol/L within ~ 18 hours on Day 5). Under the impression of EPM, we repeated the brain MRI one week after admission (Fig. 2) and the results suggested demyelinating

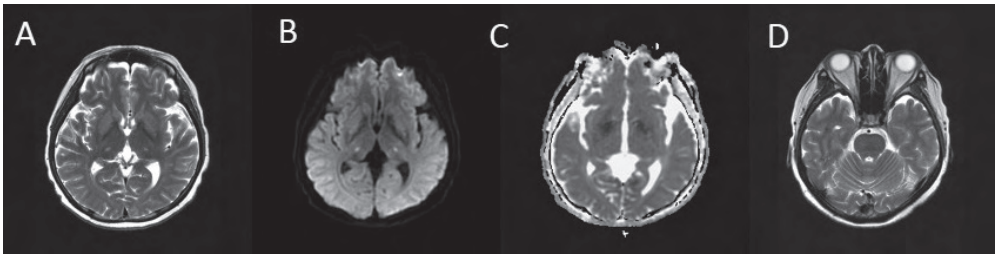

Figure 1. The brain MRI on Day 30
T2-weighted imaging (Panel A) showed bilateral thalamic high-signal lesions. The diffusion weighted imaging (Panel B) and apparent diffusion coefficient map (Panel C) revealed a diffusion restriction pattern in the bilateral thalamus. The T2-weighted imaging revealed no abnormalities of the pons (Panel D).

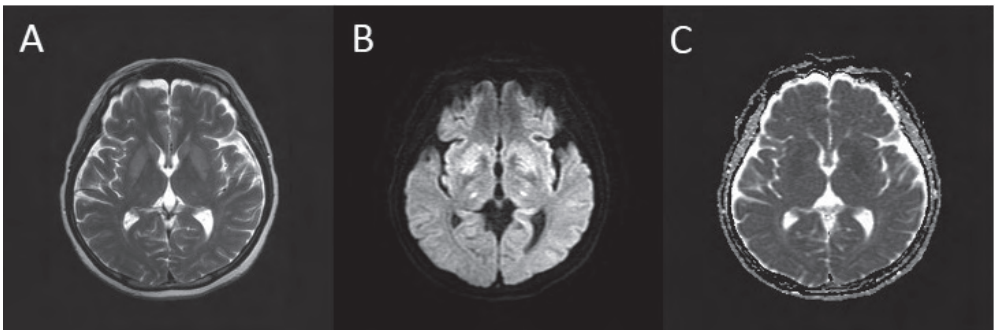

Figure 2. The brain MRI on Day 38
The T2-weighted image (Panel A) revealed bilateral thalamus and a newly developed striatum high signal compared with the previous brain MRI. The diffusion weighted image (Panel B) and the apparent diffusion coefficient map (Panel C) revealed a diffusion restriction pattern at the bilateral thalamus and striatum.

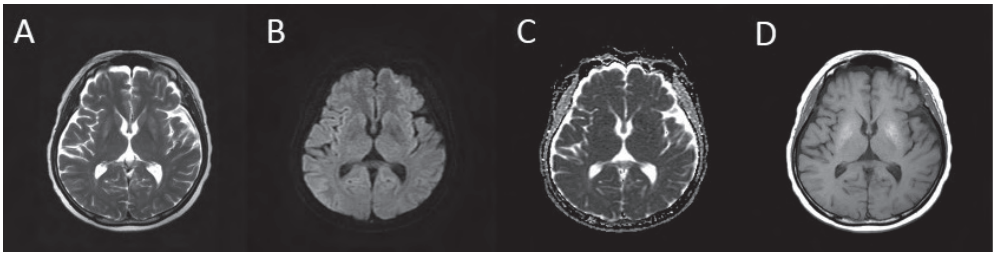

Figure 3. The follow-up brain MRI on Day 112 (3 months after symptoms onset)
The T2-weighted image (Panal A) revealed a residual high signal at the bilateral striatum, markedly decreased compared to the previous brain MRI on Day 30 of symptoms onset. The diffusion weighted image (Panal B) and apparent diffusion coefficient map (Panel C) revealed no diffusion restriction pattern at the bilateral thalamus and striatum. T1-weighted image (Panal D) revealed a high signal at the bilateral striatum, suggesting microhemorrhage or mineral deposits

lesions expanding from the bilateral thalamus initially to the bilateral striatum. The nature of the demyelination was further confirmed by MRS (Day 38) showing reduced NAA/Cr (1.031) and Cho/Cr (0.276) ratios. She did not receive specific treatment for EPM. However, steroid treatment was introduced for her adrenal insufficiency, starting from intravenous hydrocortisone 60 mg daily then shifting to oral cortisol acetate 75 mg daily 3 days later. She was discharged with no parkinsonism and her speech returned to normal around 2 months after symptom onset. After discharge, she was able to carry out daily activities by herself. She visited our neurology clinic for follow-up about 3 months after the onset of symptoms, and neurological examinations revealed no parkinsonism or dysarthria. A follow-up brain MRI on Day 112 (Fig. 3) showed resolved T2-hyperintensities, which correlated with clinical improvement. The follow-up brain MRS at the same time also revealed restored NAA/Cr (1.216) and Cho/Cr (0.3311) ratios.

DISCUSSION

This patient presented with parkinsonism and dysarthria about 3 weeks after rapid correction of hyponatremia secondary to adrenal crisis. The serial brain MRIs and MRS of this patient showed bilateral

thalamic and striatal lesions, and the differential diagnosis included liver diseases, Creutzfeldt-Jakob disease, Fahr disease, Wilson disease, EPM, non-ketotic hyperglycemia, hypoglycemia, toxic poisoning (carbon monoxide, methanol, and cyanide), and CNS toxoplasmosis [5] . After a serial MRI, blood tests, cerebrospinal fluid analysis, and history taking, we confirmed EPM as the final diagnosis. Of note, our patient had no risk factors for ODS, such as alcoholism, malnutrition, prolonged diuretic usage, psychogenic polydipsia, burns, liver transplant, and pituitary surgery. After steroid treatment, the patient recovered well and follow-up brain MRI 3 months after symptom onset showed a return to normal.

1. Diagnostic pitfalls of ODS

The present case implicates 3 pitfalls that may delay the diagnosis of ODS. The first is the diverse clinical presentations of ODS, which may mimic other neurological disorders. The clinical presentation of ODS varies with lesion localization. CPM usually presents with consciousness disturbance, tetraparesis, bulbar palsy, or a locked-in status. EPM may involve the cerebellum (55%), lateral geniculate body (41%), putamen (34%), thalamus (34%) or cerebral cortex/subcortex (34%), [2,4] and may develop a more diverse symptomatology, including emotional liability, ataxia, tremor, myoclonus, akinetic mutism, catatonia, dystonia, choreoathetosis or parkinsonism [6]. The constellation of symptoms in our patient echoes the complex nosology of ODS.

Second, a history of hyponatremia with subsequent rapid correction is a typical reminder of ODS, but may be lacking or uncertain at the initial diagnosis. As in this case, heightened alertness plus confirmation of pertinent medical histories can prevent diagnostic delay.

Third, there may be a time lag between symptom onset and significant MRI changes in ODS patients. In our patient, the brain MRI revealed only small DWI and T2 hyperintensities in the bilateral thalamus at admission (10 days after symptom onset), which progressed to explicit striatal demyelination one week later. The time sequence of the brain MRI changes was consistent with previous reports. In a United States study, brain MRI in ODS showed typical hyperintense lesions in traditional T2-weighted and fluid-attenuated inversion recovery (FLAIR) images around 1-2 weeks after symptoms onset [7]. Of note, recent evidence showed that DWI can detect the diffusion restriction of ODS within 24 hours of symptoms onset, which suggests DWI along with apparent diffusion coefficient (ADC) maps are useful for early diagnosis [8]. Therefore, those patients with suspicious ODS warrant an early brain MRI with DWI sequences and ADC maps to reaffirm the early diagnosis of ODS.

2. The benefit of brain MRS in the diagnosis of ODS

It is unknown whether MRS is beneficial for early diagnosis of ODS since our patient did not undergo MRS studies within 2 weeks of disease onset. However, a study investigating MRS longitudinal changes in CPM after liver transplantation showed an abnormal pattern compatible with demyelination as early as 8 days after disease onset, which persisted and progressed in the follow-up study 48 days after disease onset [9]. In the present case, there was notable parallel improvement in clinical deficits and MRS abnormalities. It is thus worthwhile to elucidate the clinical value of MRS in clinical follow-up or prognostic prediction of ODS in future studies.

3. Adrenal insufficiency, hyponatremia and ODS

The pathophysiology of ODS is not clear to date. The risk factors associated with ODS include alcoholism, malnutrition, liver transplantation, prolonged diuretic use, psychogenic polydipsia, burns and post-pituitary surgery, most of which are linked to an underlying hyponatremia[4]. In a hyponatremic status, brain cells pump out osmoles (potassium and sodium salts, and organic osmoles) to establish a new osmotic equilibrium ("adaptation status") across the plasma membrane. Therefore, it is proposed that an overly aggressive therapy with hypertonic saline would abolish the adaptation status, which turns out to be the culprit of ODS [10]. Osmotic change in rats can damage astrocytes and further disrupt the blood-brain barrier (BBB) or tight junctions of the brain [11-13]. Subsequent extravasation of immunoglobulins, complement proteins, cytokines and vasoactive amines further results in oligodendroglial injury, which breaks down myelin basic proteins (MBP) leading to ODS [12,13].

There have been 9 patients with adrenal insufficiency, including the present case, reported to develop ODS (Table). Although adrenal insufficiency is not designated as a risk factor for ODS [2], there may be a pathophysiological

link between adrenal insufficiency and ODS. In rat studies, steroid can prevent BBB disruption and subsequent MBP damage [13]. Therefore, patients with adrenal insufficiency may be particularly vulnerable to ODS due to a lack of the protective effect of steroid during osmotic change [12,14]. In line with this assumption, 2 reported patients with adrenal insufficiency (Table) still developed ODS despite a standard rate of sodium replacement.

Of note, all 9 patients with adrenal insufficiency (Table) presented with EPM rather than CPM, with striatal involvement in all patients except for the 2 who lacked pertinent information of lesion localization [15]. It is unknown whether patients with adrenal insufficiency are especially vulnerable to EPM rather than CPM. Nevertheless, previous studies on rat CNS revealed higher densities of glucocorticoid receptors at the basal ganglia and hippocampus than at the white matter and other cerebral regions [16] . Given the protective role of steroid on glia cells during osmotic disequilibrium, a heterogeneous distribution of glucocorticoid receptors may explain why patients with primary adrenal insufficiency tend to develop EPM rather than CPM in the ODS spectrum.

A clinical recovery at 2 months and a normal MRI follow up at 3 months of symptoms onset in the present case was a better outcome than that of other patients with ODS [17,18]. In a recent case series of isolated EPM presenting with transient parkinsonism, the majority of patients did not show good recovery until follow-up at 4 months to 4 years [18]. The only patient who had recovered well at the 2-month follow-up also suffered from adrenal

Table. Review of cases presenting isolated EPM with adrenal insufficiency

Case report	Country	Underlying Condition	Rapid correction of hyponatremia (>10 mmol/L in 24 hr)	Clinical Presentation	Brain Imaging
The present case	Taiwan	Primary adrenal insufficiency	Yes	Dysarthria, parkinsonism	Day 13 of symptom onset: T2 & DWI high signal in the bilateral thalamus Day 21: T2 & DWI high signal in the bilateral striatum and thalamus
Imam et al., 2012[21]	Oman	Panhypopituitarism with rapid correction of hyponatremia	Yes	Parkinsonism	T2 & FLAIR high signal in the bilateral striatum, thalamus and anterior temporal lobes
Gujjar et al., 2010[22]	Oman	Addison's disease with systemic tuberculosis	No, Na raised from 119 to 124 mmol/L on Day 6, 134 mmol/L on Day 14	Reversible parkinsonism	Symptoms onset (Day 1): normal Day 21: T2 & FLAIR high signal in the bilateral basal ganglia
Al-Mamari et al., 2009[23]	Oman	Secondary adrenal insufficiency	Hyponatremia, how rapid the correction was not mentioned	Partially reversible parkinsonism	On admission: normal Two weeks later: T2 high signal in tha bilateral basal ganglia
Srimanee et al., 2009 [15]	Thailand	Secondary adrenal insufficiency	Yes	Dystonia	"Compatible with EPM" but localization not described
Srimanee et al., 2009 [15]	Thailand	Secondary adrenal insufficiency	Unknown	Dystonia, dysarthria	"Compatible with EPM" but localization not described
Okada et al., 2005 [24]	Japan	Secondary adrenal insufficiency	Yes, Na raised 15 mmol in one day	Reversible parkinsonism,	On admission (Day 1): normal Day 13: T2 high signal in the bilateral striatum
Lasheen et al., 2005 [25]	Kuwait	Secondary adrenal insufficiency	Yes, Na raised 30 mmol/L in 48 hours	Agitation, dysarthria	T2 high signal in bilateral striatum
Sajith et al., 2006 [26]	United Kingdom	Addison's disease	No, Na raised from 100 mmol/L to 130 mmol/L in 5 days	Parkinsonism	Initial: T2 high signal in the bilateral striatum Two months later: resolution

insufficiency (Addison's disease) once treated with steroid. Whether such a coincidence echoes the above-mentioned protective effect of steroid in ODS remains to be determined; however, some authors did suggest introducing steroids before sodium correction in severely hyponatremic patients to prevent the development of ODS [19]. Further studies are needed to investigate if the beneficial effect of steroid can be faithfully translated to the treatment or even prevention of ODS in patients with or without adrenal insufficiency. The optimal dosing of steroid to prevent ODS, especially in patients with adrenal insufficiency, also merits further investigation since the present case developed ODS while she was taking oral steroid in an adequate dose for adrenal insufficiency per se [20].

CONCLUSION

Development of acute parkinsonism in patients with hyponatremia after rapid correction may indicate the occurrence of ODS, especially EPM, and underlying adrenal insufficiency should be excluded. EPM may develop in patients with adrenal insufficiency even in the absence of a history of rapid sodium replacement. Steroid may be beneficial for the treatment and prevention of ODS in susceptible patients with adrenal insufficiency.

Funding: This study was supported in part by research grants from Taipei Veterans General Hospital, Taipei (V102C-103) and Veterans General Hospitals and University System of Taiwan (VGHUST102-G7-6-2).

REFERENCES

1. Adams RA, Victor M, Mancall EL. Central pontine myelinolysis: a hitherto undescribed disease occurring in alcoholics and malnourished patients. AMA Arch Neurol Psychiatry 1959;81:154-172.
2. Karp BI, Laureno R. Central pontine and extrapontine myelinolysis after correction of hyponatraemia. The Neurologist 2000;6:255-266.
3. Gocht A, Colmant HJ. Central pontine and extrapontine myelinolysis: a report of 58 cases. Clin Neuropath 1987;6:262-270.
4. Martin RJ. Central pontine and extrapontine myelinolysis: The osmotic demyelination syndromes. J. Neurol Neurosurg Psychiatry 2004;75:22-28.
5. Hegde AN, Mohan S, Lath N, Lim CC. Differential diagnosis for bilateral abnormalities of the basal ganglia and thalamus. Radiographics 2011;31:5-30.
6. Aaron de Souza. Movement disorders and the osmotic demyelination syndrome. Parkinsonism Relat Disord 2013;19:709-716.
7. Howard SA, Barletta JA, Klufas RA, Saad A, De Girolami U. Best cases from the AFIP: osmotic demyelination syndrome. Radiographics 2009;29:933-938.
8. Ruzek KA, Campeau NG, Miller GM. Early Diagnosis of Central Pontine Myelinolysis with Diffusion-Weighted Imaging. AJNR Am J Neuroradiol 2004;25: 210-213.
9. Guo Y, Hu JH, Lin W, Zheng KH. Central pontine myelinolysis after liver transplantation: MR diffusion spectroscopy and perfusion finding. Magn Reson Imaging 2006;24:1395-1398.
10. Vaidya C, Ho W, Freda BJ. Management of hyponatremia: providing treatment and avoiding harm. Cleve Clin J Med 2010;77:715-726.
11. Gankam Kengne F, Nicaise C, Soupart A, Boom A, Schiettecatte J, Pochet R, Brion JP, Decaux G. Astrocytes Are an Early Target in Osmotic Demyelination Syndrome. J Am Soc Nephrol 2011;22:1834-1845.
12. Sugimura Y, Murase T, Takefuji S, Hayasaka S, Takagishi Y, Oiso Y, Murata Y. Protective effect of dexamethasone on osmotic-induced demyelination in rats. Exp Neurol 2005;192:178-183.
13. Dobrogowska DH, Vorbrodt AW. Immunogold localization of tight junctional proteins in normal and osmotically-affected rat blood-brain barrier. J Mol Histol 2004;35:529-539.
14. Adrogué HJ, Madias NE. Hyponatremia. N Engl J Med 2000;342:1581-1589
15. Srimanee D, Bhidayasiri R, Phanthumchinda K. Extrapontine myelinolysis in preoperative sellar region tumor: report of two cases. J Med Assoc Thai 2009; 92:1548-1553.
16. Sánchez MM, Young LJ, Plotsky PM, Insel TR. Distribution of Corticosteroid Receptors in the Rhesus Brain: Relative Absence of Glucocorticoid Receptors in the Hippocampal Formation. J Neurosci 2000;20:4657-4668.

17. Post B, van Gool WA, Tijssen MA. Transient Parkinsonism in isolated extrapontine myelinolysis. Neurol Sci 2009;30:325-328.
18. Kallakatta RN, Radhakrishnan A, Fayaz RK, Unnikrishnan JP, Kesavadas C, Sarma SP. Clinical and functional outcome and factors predicting prognosis in osmotic demyelination syndrome (central pontine and/or extrapontine myelinolysis) in 25 patients. J Neurol Neurosurg Psychiatry 2011;82:326-331.
19. Kleinschmidt-DeMasters BK, Rojiani AM, Filley CM. Central and extrapontine myelinolysis. Then… and now. J Neuropathol Exp Neurol 2006;65:1-11.
20. Neary N, Nieman L. Adrenal Insufficiency-etiology, diagnosis and treatment. Curr Opin Endocrinol Diabetes Obes 2010;17:217-223.
21. Imam YZ. Extrapontine Myelinolysis-Induced Parkinsonism in a Patient with Adrenal Crisis. Case Rep Neurol Med 2012;2012:327058.
22. Gujjar A, Al-Mamari A, Jacob PC, Jain R, Balkhair A, Al-Asmi A. Extrapontine myelinolysis as presenting manifestation of adrenal failure: a case report. J Neurol Sci 2010;290:169-171.
23. Al-Mamari A, Balkhair A, Gujjar A, Ben Abid F, Al-Farqani A, Al-Hamadani A, Jain R. A case of disseminated tuberculosis with adrenal insufficiency, Sultan Qaboos Univ Med J 2009;9:324-327.
24. Okada K, Nomura M, Furusyo N, Otaguro S, Nabeshima S, Hayashi J. Amelioration of extrapontine myelinolysis and reversible Parkinsonism in a patient with asymptomatic hypopituitarism. Intern Med 2005;44:739-742.
25. Lasheen I, Doi SA, Al-Shoumer KA. Glucocorticoid replacement in panhypopituitarism complicated by myelinolysis. Med Princ Pract 2005;14:115-117.
26. Sajith J, Ditchfield A, Katifi HA. Extrapontine myelinolysis presenting as acute parkinsonism. BMC Neurol 2006;6:33.