Myotonic dystrophy type 1 accompanied with normal pressure hydrocephalus: a case report and literature review

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Abstract

Background: Myotonic dystrophy type 1 (DM1) is the most common disease that can cause muscle weakness and atrophy among adults. Normal pressure hydrocephalus (NPH) is characterized by the triad of gait disturbance, cognitive impairment and urinary incontinence. The association between DM1 and NPH is extremely rare. We report a Chinese female patient with DM1 in association with NPH.

Case presentation: The patient presented with a history of 3-year of walking instability and cognitive impairment. Her brain MRI showed ventriculomegaly with normal cerebrospinal fluid (CSF) pressure and the CSF tap-test was positive, which indicated the diagnosis of probable NPH. DM1 was confirmed by genetic testing.

Conclusions: Four patients with DM1-NPH association were found before. The association between NPH and DM1 may not be just a coincidence, NPH may occur in DM1 later in life and it is vital to recognize the association as a shunt surgery may improve patients’ quality of life.

Keywords: Myotonic dystrophy (DM1), Normal pressure hydrocephalus (NPH), Genetic testing, Muscular dystrophy

Background

Myotonic dystrophy type 1 (DM1) is the most common type of muscular dystrophy in adult. It is an autosomal dominant disease which is associated with abnormal expansion of the repeated cytosine-thymine-guanine (CTG) in the 3’-untranslated regions in dystrophia myotonica-protein kinase (DMPK) gene on chromosome 19q13.3 [1]. In DM1, CTG invariably repeats for over 50 times. The disease can occur from infants to adults with the mean age of onset being in the third decade of life [2]. While the symptoms of DM1 are polymorphous [3, 4], myotonia and muscular weakness are typical clinical features, primarily affecting facial and distal limb muscles. DM1 can involve multiple systems, such as cataracts, gastrointestinal symptoms, cardiac conduction defects, hypogonadism, endocrine function impairment, and brain abnormalities [1, 5, 6]. In addition, expectation of life is markedly decreased, primarily due to aspiration pneumonia or cardiac arrhythmias [7, 8].

Normal pressure hydrocephalus (NPH) is a neurological disease characterized by the triad of gait disturbance, cognitive impairment and urinary incontinence, presenting ventriculomegaly and normal cerebrospinal fluid (CSF) pressure. It was initially described in 1965 and can be treated via ventriculoperitoneal shunt surgery [9–11]. The prevalence of probable NPH was 0.2% in people aged 70–79 years and 5.9% in those aged 80 years and older [12]. According to the American-European NPH guidelines [13], NPH can be classified into probable, possible, and unlikely categories. Probable NPH is diagnosed by hydrocephalic ventricular enlargement together with gait disturbance and either cognitive impairment or urinary incontinence.

The coexistence of myotonic dystrophy (DM) and NPH has been reported in four patients so far (Table 1) [14–16]. But none of them were confirmed by genetic testing or muscular biopsy. Here, we present a Chinese female patient with DM1 confirmed by genetic testing in association with NPH and conduct a review of the literature in
order to determine clinical specific features of this co-
occurrence and the possible mechanisms.

Case presentation
A 65-year-old Chinese woman with 1 year of grade
school education came to the Department of Neurology,
First Affiliated Hospital of Zhejiang University in No-
vember 2018. Her complaints included a 3-year history
of walking instability which was characterized by slow
walking, lower foot height, hypokinesis, poor balance,
reduced stride length, broad-based gait, and difficult
starting/turning. Furthermore, she was found to have
memory loss and was slow to respond. The symptoms
had gradually worsened, and she was dependent on fam-
ily members to help her walk. Twenty days before pre-
senting to our clinic, she suffered thoracic vertebral
compression fracture (T11–12) due to a fall at home
and required surgery. The patient had no medical his-
tory of hypertension, diabetes, cardiac diseases. She had
no family history of similar diseases. Her neurological
examination revealed a severe gait disturbance and in-
creased muscular tone of limbs. Marked muscle wasting
was seen in the temporalis. The Medical Research Coun-
sil power was 4/5 on the flexor and extensor of four
limbs (Fig. 1a-c). Neuropsychological examination re-
vealed diminished memory, prominent math difficulties
and temporal-space disorientation. She scored 7/30 on
the MMSE (Table 2). No abnormalities in the cranial
nerves and sensory system were noted.

Additional screens detected no abnormalities, including
normal routine blood tests, biochemistry examination, co-
agulation function, thyroid function, tumor marker, and
normal folate and vitamin B12 levels. Screens for HIV,
syphilis and hepatitis were negative. Furthermore, routine
CSF analysis, CSF biochemistry and CSF pressure were nor-
mal. However, first degree atroioventricular block and
complete right bundle branch block was presented in the
electrocardiogram (ECG), cholecystolithiasis in abdominal
ultrasound, bilateral multiple thyroid nodules in the thyroid
ultrasound, and chronic inflammatory foci in the lower
lobes of both lungs in lung CT. Furthermore, brain MRI re-
vealed ventriculomegaly (Evans index =0.34) (Fig. 1d)
and atrophy on bilateral frontal, temporal and occipital lobes
(Fig. 1e-f). Moreover, the electromyogram (EMG) indicated
muscle damage with excessive myotonic discharge. Finally,
genetic testing showed an over 100 CTG repeat expansion
in the DMPK gene on chromosome 19q13.3, confirming
the diagnosis of DM1 (Fig. 1g). Her two children also
underwent genetic testing and one daughter presented with
a repeat expansion on the DMPK gene.

As noted previously, the patient demonstrated gait dis-
turbance and cognitive impairment (in absence of urinary
incontinence) accompanying with normal CSF pressure
and ventricular enlargement. These observations triggered
a probably case of NPH [17] and cerebrospinal fluid tap-
test (CSF-TT) was performed. The patient’s gait tempo-
arily improved after CSF drainage (Table 3). A second
CSF-TT was performed with a similar pattern of tempo-
rary gait improvements (Table 3). These observations are
consistent with NPH, further suggesting the diagnosis of
NPH. However, the patient refused shunt surgery and was
discharged. A 6-month follow-up showed aggravation of
symptoms and increased dependence on family members.

Discussion and conclusions
Currently, the definite diagnosis of DM1 is made by
DNA analysis. By contrast, in the past, non-molecular
testing has been widely adopted which plays no role now
[18] due to its inaccuracy. We searched Pubmed (index
1965–2016) for similar cases. An association between
NPH and DM1 has been noted in 4 other cases, (Table 1)
[14–16], although no definitive genetic testing for DM1
was conducted in previous case studies. Here we de-
scribe a case with genetically confirmed DM1 and NPH.

### Table 1 Summary of five cases associating myotonic dystrophy (DM) and normal pressure hydrocephalus (NPH)

| Year/Author | Gender | Onset age | Symptoms | Testing | Treatment | Improvement |
|-------------|--------|-----------|----------|---------|-----------|-------------|
| 1985, Riggs | F      | 50        | +        | +       | Obvious hydrocephalus | / |
| 1988, Christensen | F      | 61        | +        | +       | Ventricular enlargement | / |
| 1988, Christensen | M      | 75        | +        | +       | Ventricular enlargement | / |
| 2006, Delavalle | M      | 61        | No urinary incontinence | +   | Evans index 0.41 | / |
| Present case | F      | 62        | No urinary incontinence | +   | Evans index 0.34 | / |

ICP intracranial pressure; /, data not available; +, positive
Genetic testing showed that the patient had 100 CTG repeats in the DMPK gene. Consistent with a clinical presentation of DM1, the patient exhibited muscular weakness, muscle wasting of temporal and distal limb muscles. Additionally, myogenic damage and excessive myotonic discharge were noted on the EMG. For the last 3 years, she had experienced progressive gait disturbance and cognitive decline. Brain MRI showed enlarged ventricles with an Evans index of 0.34, indicating ventricular enlargement. MRI scans showed atrophy on bilateral frontal, temporal and occipital lobes. DNA analysis indicated that CTG repeated over 100 times.

Table 2 Results of MMSE

| Item                  | Evaluation score |
|-----------------------|------------------|
| Orientation to time   | 0/5              |
| Orientation to place  | 2/5              |
| Registration          | 1/3              |
| Attention and calculation | 0/5              |
| Recall                | 0/3              |
| Naming                | 2/2              |
| Repetition            | 0/1              |
| Reading               | 1/1              |
| Writing               | 0/1              |
| Complex commands      | 1/3              |
| Drawing               | 0/1              |
| Total                 | 7/30             |

MMSE mini-mental state examination

Genetic testing showed that the patient had 100 CTG repeats in the DMPK gene. Consistent with a clinical presentation of DM1, the patient exhibited muscular weakness, muscle wasting of temporal and distal limb muscles. Additionally, myogenic damage and excessive myotonic discharge were noted on the EMG. For the last 3 years, she had experienced progressive gait disturbance and cognitive decline. Brain MRI showed enlarged ventricles with an Evans index of 0.34 and CSF pressure was normal. Ventricular enlargement in the presence of normal CSF pressure pointed to NPH [17], which was supported by two positive CSF-TT. NPH can be confirmed with ventriculoperitoneal shunting, unfortunately, our patient refused treatment.

DM1 brains show general atrophy and widespread gray matter volume reductions [19]. It is well established that DM1 affected central nervous system including cognitive
and psychiatric dysfunction [20–30]. Deficits in several cognitive domains have been reported, including executive function, memory, visuospatial problems, processing speed and attention [20–25]. These deficits appear to worsen as patient's age. For instance, Sansone et al. [22] found frontal cognitive impairment worsens over time and two recent longitudinal studies have observed a progression of cognitive impairment, particularly in verbal memory, visuospatial function, attention and processing speed [31, 32]. However, the degree of decline has no correlation with the repetition number of CTG or the severity of muscular involvement [21, 31, 32]. In addition to cognitive impairments, several studies have described psychiatric disturbances in DM1 patients such as anxiety, depression, apathy, anosognosia, paranoid and aggressive traits in DM1 [20, 26–30, 33, 34]. Several psychiatric disorders such as anxiety are negatively correlated with level of education and the number of CTG repeats [30].

Cerebral ventriculomegaly is commonly reported in DM1 patients [35–37] and appears to be progressive [35]. Glantz et al. [36] reported an increased incidence (71.4%) of ventriculomegaly in DM1 patients. Neuroimaging studies using DTI and VBM have revealed extensive white and gray matter damage among DM1 patients. Brain abnormalities have been linked with the number of CTG repeats, cognitive function and muscle weakness [38–47].

The mechanism of NPH may be the obliteration of arachnoid villi (small protrusions of the arachnoid mater which can return CSF to the venous circulation), leading to the disturbances of CSF reabsorption, leading to disrupted CSF reabsorption and subsequent ventricular enlargement [48, 49]. The possible mechanism of NPH in DM1 patients may be related to widespread cell membrane defects caused by genetic abnormalities [14], leading to the arachnoid granulations [48, 50, 51]. However, the association between DM1 and NPH can be overlooked for several reasons. One might be NPH tends to occur in elderly DM1 patients, and other reasons could be that cardinal symptoms of NPH, e.g. cognitive impairment, disturbance of gait and urinary incontinence, are common in the elderly and therefore ignored as nonspecific. Mathieu and Prevost found that the mean age at death was 55.4 years for the adult-onset phenotype of DM [7]. Furthermore, according to Smulders et al. [52], the survival rate of adult-onset type of DM1 who lives to the ages 25, 45 and 65 years is 99, 88 and 18%, in comparison to the expected survival rates for unaffected adults, which are 99, 95 and 78%, respectively. Therefore, the probability of adult-onset DM1 patients living to 65 years of age is significantly reduced. Our patient is now 65 and patients with NPH in association with DM1 appear to be more than 50 years old (Table 1), suggesting DM1 may result in NPH later in life.

Two of the four patients with DM1-NPH association received shunt surgery (Table 1) and were markedly improved. Although our patient refused to be treated with ventriculoperitoneal shunt, her symptoms were ameliorated after CSF drainage (Table 3), also indicating that shunt surgery is an effective therapy.

Overall, for elderly patients with DM1 presenting symptoms of gait disturbance or urinary incontinence, it is vital to consider the association of NPH. Once DM1-NPH association is considered, shunt surgery should be suggested and the patient should be transferred to neurosurgery department. In this way, it could improve the patients’ quality of life.

**Abbreviations**

CSF: Cerebrospinal fluid; CST-TT: Cerebrospinal fluid tap-test; CTG: Cytosine-thymine-guanine; DM1: Myotonic dystrophy type 1; DMPK: Dystrophia myotonica-protein kinase; ECG: Electrocardiogram; EMG: Electromyogram; MMSE: Mini-Mental State Examination; NPH: Normal pressure hydrocephalus

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**Authors’ contributions**

JYW and ML are responsible for data collection, analysis, and for drafting and finalizing the manuscript. WJS and ZQC are responsible for data collection and analysis. GPP is responsible for revising the manuscript, analysis, and interpretation of data. All authors have read and approved the manuscript.

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**Availability of data and materials**

All data generated or analysed during this study are included in this published article.

**Ethics approval and consent to participate**

Not applicable.

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**Table 3** Results of cerebrospinal fluid tap-test by using 10-m walking test

|                  | First evaluation | Second evaluation |
|------------------|------------------|-------------------|
|                  | Before drainage  | 6 h after drainage| Before drainage  | 6 h after drainage |
| Steps            | 85               | 79 (7%†)          | 75               | 62 (17%†)          |
| Time (s)         | 137              | 95 (30%‡)         | 68               | 51 (25%‡)          |

† means improvement

|                  | Before drainage  | 6 h after drainage |
|------------------|------------------|-------------------|
| Steps            | 85               | 79 (7%†)          |
| Time (s)         | 137              | 95 (30%‡)         |

Before drainage 6 h after drainage Before drainage 6 h after drainage

First evaluation Second evaluation

|                  | Steps | Time (s) |
|------------------|-------|----------|
| Before drainage  | 85    | 137      |
| 6 h after drainage| 79    | 95       |

|                  | Steps | Time (s) |
|------------------|-------|----------|
| Before drainage  | 75    | 68       |
| 6 h after drainage| 62    | 51       |

|                  | Steps | Time (s) |
|------------------|-------|----------|
| Before drainage  | 75    | 68       |
| 6 h after drainage| 62    | 51       |
40. Caso F, Agosta F, Peric S, Rakočević-Stojanović V, Copetti M, Kostic VS, et al. Cognitive impairment in myotonic dystrophy type 1 is associated with white matter damage. PLoS one. 2014;9(8):e104697. https://doi.org/10.1371/journal.pone.0104697.

41. Schneider-Gold C, Bellenberg B, Prehn C, Krogius C, Schneider R, Klein J, et al. Cortical and Subcortical Grey and White Matter Atrophy in Myotonic Dystrophies Type 1 and 2 Is Associated with Cognitive Impairment, Depression and Daytime Sleepiness. PLoS one. 2015;10(6):e0130352. https://doi.org/10.1371/journal.pone.0130352.

42. Serra L, Petrucci A, Spanò B, Torso M, Olivito G, Lisi L, et al. How genetics affects the brain to produce higher-level dysfunctions in myotonic dystrophy type 1. Funct Neurol. 2015;30(1):21–31.

43. Weber YG, Roebling R, Kassubeck J, Hofmann S, Rosenbohm A, Wolf M, et al. Comparative analysis of brain structure, metabolism, and cognition in myotonic dystrophy 1 and 2. Neurology. 2010;74(14):1108–17. https://doi.org/10.1212/WNL.0b013e3181d8c35f.

44. Wozniak JR, Mueller BA, Bell CJ, Muetzel RL, Lim KO, Day JW. Diffusion tensor imaging reveals widespread white matter abnormalities in children and adolescents with myotonic dystrophy type 1. J Neurol. 2013;260(4):1122–31. https://doi.org/10.1007/s00415-012-6771-4.

45. Wozniak JR, Mueller BA, Lim KO, Hemny LS, Day JW. Tractography reveals diffuse white matter abnormalities in Myotonic dystrophy type 1. J Neurol Sci. 2014;341(1–2):73–8. https://doi.org/10.1016/j.jns.2014.04.005.

46. Wozniak JR, Mueller BA, Ward EE, Lim KO, Day JW. White matter abnormalities and neurocognitive correlates in children and adolescents with myotonic dystrophy type 1: a diffusion tensor imaging study. Neuromuscul Disord. 2011;21(2):89–96. https://doi.org/10.1016/j.nmd.2010.11.013.

47. Zanigni S, Evangelisti S, Giannoccaro MP, Oppi F, Podà R, Giorgio A, et al. Relationship of white and gray matter abnormalities to clinical and genetic features in myotonic dystrophy type 1. Neuroimage Clin. 2016;11:678–85.

48. Raftopoulos C, Chaskis C, Deleval J, Chaskis C, Leonard A, Cantraine F, Desmyttere F, et al. Cognitive recovery in idiopathic normal pressure hydrocephalus: a prospective study. Neurosurgery. 1994;35(3):397–404 discussion –5.

49. Duinkerke A, Williams MA, Rigamonti D, Hills AE. Cognitive recovery in idiopathic normal pressure hydrocephalus after shunt. Eur Neurol. 2004;51(3):179–84.

50. Murakami Y, Matsumoto Y, Hoshi K, Itó H, Fuxua T, Yamaguchi Y, et al. Rapid increase of 'brain-type' transferrin in cerebrospinal fluid after shunt surgery for idiopathic normal pressure hydrocephalus: a prognosis marker for cognitive recovery. J Biochem. 2018;164(3):205–13. https://doi.org/10.1093/jb/mvy043.

51. de De-Smulders CE, Howeller CJ, Thijs C, Mirandolle JF, Anten HB, Smeets HJ, et al. Age and causes of death in adult-onset myotonic dystrophy. Brain. 1998;121(Pt 8):1557–63.

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