



Jacqueline du Pré and her alternative diagnosis

Takahiro Mezaki^{a,*}, Kanako Namekawa^b

^a Department of Neurology, Sakakibara Hakuho Hospital, Sakakibara-cho, Tsu City, Mie 514-1251, Japan

^b Department of Neurology, Kurashiki Central Hospital, Miwa, Kurashiki City, Okayama 710-8602, Japan



ABSTRACT

Jacqueline du Pré (26 January 1945–19 October 1987) is one of the greatest cellists in the 20th century. Her musical career was terminated at age 28, allegedly due to multiple sclerosis (MS). MS is an immune-mediated demyelinating disease of the central nervous system with axonal involvement, characterized by the dissemination in time and space of the lesions (plaques). Diverse neurological symptoms may occur in MS, and a variety of symptoms relentlessly accumulated in her case after the diagnosis in 1973, which is concordant with primary progressive rather than relapsing-remitting form of MS. No radiological confirmation was however possible in her days and the diagnosis should be reconsidered, because her symptoms had some unusual features in MS. First, her principal symptoms, aside from transient visual and urological problems noticed earlier, began in the upper and lower limbs, often only in the upper limbs, then followed by the involvement of lower cranial nerves, and by the cognitive decline with changes in character. Hence the pattern of progression was ascending from the cervical spinal cord to the brainstem and to the cerebrum, which is not the pattern of dissemination in space typical of MS. Her clinical status appeared steroid-dependent temporarily in the early stage of the disease, which is also unusual in MS and some different etiology deserves consideration. We suppose that Uhthoff phenomenon, i.e. worsening of symptoms by the elevation of body temperature, may have been negative contrary to the previous interpretation, and if we are correct the absence of this sign does not support the demyelinating pathophysiology of her disease. Now that there is no objective medical information sufficiently disclosed, another scenario may be hypothesized, although MS is still a likely possibility. We discuss that syringomyelia/syringobulbia associated with Chiari malformation type I and obstructive hydrocephalus can be an alternative diagnosis.

Introduction

Jacqueline du Pré is one of the greatest cellists in the 20th century, born in Oxford, England, on 26 January 1945, and her premature death in London came on 19 October 1987, at age 42. The diagnosis was multiple sclerosis (MS).

MS is an immune-mediated demyelinating disease of the central nervous system with axonal involvement. The clinical course is typically relapsing and remitting, while symptoms may relentlessly aggravate as a primary or secondary progressive form.

In her days medical technologies were still premature as compared to those in the modern era and the diagnosis of MS was mostly based on the clinical course and symptomatology. Currently magnetic resonance imaging (MRI) is indispensable for the diagnosis of MS [1], not available at the time of her diagnosis. Hence her case deserves reconsideration.

Hypothesis

Jacqueline du Pré had a progressive disease of the central nervous system, but the diagnosis of MS is nothing but a likely possibility because of the lack of objective evidence. As an alternative,

syringomyelia, its rostral extension (syringobulbia), and hydrocephalus associated with Chiari malformation type I can also explain her symptoms and clinical course.

Clinical history

She started playing cello at age 4 and her talent flourished soon. She was world-famous already in her teens, but her career as a cellist was terminated at age 28.

When her first symptom appeared is uncertain. Her elder sister Hilary remembers that she, at age 9, told her, “Don’t tell Mum but ... when I grow up, I won’t be able to walk or move”(p. 50 [2]). There was no physical reason for this conversation, and her first possibly related symptom appeared at age 16, as some moments of blurred vision or double vision (p. 376 [3]). Transient episodes of this symptom were repeated, but in 1966 the ophthalmologist John Anderson, a music lover, scrutinized her but could find no abnormality (p. 377 [3]), without evidence of retrobulbar neuritis (p. 324 [2]). Recurrent cystitis or constant urge to urinate, which her mother Iris also had, may have started around 1965 and her family doctor Hatchick suspected neurogenic bladder, but there were no other signs of MS according to Anthony Wolf, a neurologist, when he had consultation in 1968 or 1969

* Corresponding author at: Department of Neurology, Sakakibara Hakuho Hospital, 5630 Sakakibara-cho, Tsu City, Mie 514-1251, Japan.

E-mail address: tamezaki@kuhp.kyoto-u.ac.jp (T. Mezaki).

(p. 322 [2], p. 376 [3]).

She got married with a conductor and pianist Daniel Barenboim in 1967, who recalls that du Pré “had already experienced strange symptoms like numbness in her limbs” (p. 374 [3]) in 1969. She complained of “weakness and fatigue” (p. 163 [4]), and Daniel had also impression that something was not right, remembering that she had lost weight sensation, and in 1970 she “had to get to a hall early and play for a long time so as to heat her hands sufficiently to perform” (p. 360 [3]), although formerly she did not require rehearsals. Her upper limbs were weaker than before, and her arms wouldn’t cooperate to do the large shifts (p. 364 [3]).

In 1971 she was exhausted and depressive, and her feet were numb (p. 374 [3]). Her sabbatical, having been planned independently of her condition, began on February (p. 372 [3]), and she had surgery for her twelve skin moles under general anesthesia in the University College of London (p. 320 [2], p. 374 [3]). After the surgery she complained to her general physician Selby of numb sensation. It soon affected the whole left side of her body but disappeared after a day or two (p. 320 [2], p. 375 [3]). Before this she had had episodes of unsteadiness or abnormal gait like drunkenness, and sudden ‘caving-in’ episodes of her knees caused fallings (p. 377 [3]). She could still transport the audience to an “unknown paradise” in a concert at the Inkpen Festival in July (p. 228 [2]), but the session recording of Chopin and Franck in December 1971 was to be the last in her career. When she talked with Dr. John Anderson this year, she told him, as she did in her childhood, that she knew she would be paralyzed and not able to play the cello (p. 324 [2]).

In 1972 she started to have counseling sessions from Dr. Walter Joffe. She was “experiencing patches of numbness on her arms and legs”, and “later on the soles of her feet became affected” likewise, which Joffe regarded as an “unconscious resistance” (p. 237 [2]). Before the end of this year she had to follow her fingers and bows with her eyes to play, and the critics began to notice the decline of her vitality and techniques (p. 239 [2], p. 395 [3], p. 165 [4]).

In late February 1973 she was to perform Brahms’ Concerto for Violin, Violoncello and Orchestra, opus 102, with Pinchas Zukerman, Leonard Bernstein, and the New York Philharmonic [5]. At the time of rehearsal she found that she couldn’t open her cello case by herself and she “couldn’t feel the strings of the cello or properly command the bow” (p. 166–7 [4]). Her left hand was completely numb (p. 244 [2]). According to Eugenia Zukerman, du Pré consulted a doctor already before the first concert, but her symptoms were dismissed as “hysterical” (p. 398 [3]) or “just stress” (p. 244 [2]). Four concerts had been planned on the 22th, 23th, 24th and 27th, but the third one was a “nightmare experience” (p. 398 [3]) for her and the last concert was cancelled, reportedly by the New York Times due to paresthesia of the right arm (p. 399 [3]). She had medical examinations both in the U.S. (Bernstein helped her) and also in her country, but Dr. Selby could find nothing specifically wrong although now he was beginning to suspect a neurological disorder (p. 399 [3]).

After around this time both her upper and lower limbs gradually lost their function, although symptoms were often inconsistent and even came and went away suddenly. In October she admitted the Lindo Wing of St. Mary’s Hospital, Paddington, and the clinical diagnosis of MS was made. The senior neurologist for her was Harold Edwards (p. 401 [3]).

Corticosteroids were started. When she stopped taking them she worsened quickly (p. 256 [2], p. 410 [3]), and her general status continued to aggravate so much that her first wheelchair was purchased in the end of 1974 (p. 414 [3]). In May 1975 she went to New York to admit to the Rockefeller Institute Hospital (p. 179 [4]). On admission she could still walk, but there was no improvement and after three weeks she could not walk any more, and before June she became incontinent. She went back to London on 20 June, and in late autumn of this year (p. 428 [3]) she had acute aggravation of her status. The dose of corticosteroids was increased, and her husband Daniel was called back to London because her life expectancy was estimated as only two months (p. 415 [3]). There is no information about whether this was a relapse

or the adrenal insufficiency due to abrupt discontinuation of corticosteroids, as is occasionally the case in steroid users, but she seems to have recovered from this critical condition before long, implying the latter possibility.

Her intelligence was kept preserved at latest before 1976. In 1977 her attention started to decline, but her master class for cellists at the South Bank Festival in 1978 was successful with great authority (p. 419 [3]). After this year, her short time memory and affection control deteriorated with further decline of her physical functions including limb control and articulation and her head was wobbling (p. 277 [2]). Although her narration for “Peter and the Wolf” (Prokofiev) recorded in October 1979 was beautifully performed [6], her speech became slurred by the end of this year, making sustained conversation difficult. She had not lost her sense of humor, but her personality was changing and she could be quite scornful to her students as well as to her family (p. 279 [2], p. 420 [3]). Sudden physical exacerbations occurred, and after each attack she never completely regained the function she had had before the attack (p. 200 [4]). Her diction of the verse by Ogden Nash for the performance of “Le Carnaval des Animaux” (Saint-Saëns) with Sir Charles Mackerras and the English Chamber Orchestra “was getting blurred and she was on the verge of collapsing into euphoric giggles” (p. 428–9 [3]), indicating pseudobulbar affect, which was the problem for rehearsing her readings in the same year’s Upottery Festival (p. 434 [3]), but it “was a huge success and she read the poem beautifully, as though she were playing the cello” (p. 283 [2]). Likewise, the interview with Christopher Nupen recorded on December 13, 1980, shows that her speech remained still mostly preserved [7]. However, dysarthria, dysphagia, and upper limb tremor became more and more serious, and she had to keep her arms folded to restrain the tremor (p. 435 [3]). Severe blurred vision and head tremor made it impossible for her to read or to watch television (p. 203 [4]), and by 1983 her vision was severely blurred and she became bed-bound, required total care, and the communication was now difficult because of severe dysarthria, nevertheless she “could still recite long poems from memory” (p. 210 [4]) and her musical memory remained unimpaired until the end of her life (p. 417 [3]). She and Hilary could fling jokes back and forth even in 1987 (p. 297 [2]), indicating her intelligence was at least partly undamaged until the last time of her life. Her head was constantly dipping and bouncing (p. 297 [2]), and her generalized involuntary movements caused emaciation. She repeated pneumonia and passed away at 20:30 [8], 19 October 1987 (p. 302 [2]).

Clinical investigations

In 1973 computer tomography (CT) was barely at dawn, and MRI became clinically available in 1980’s. There is no information whether she had CT or MRI study, or whether she had any electrophysiological study. The results of blood and cerebrospinal fluid study remain uncovered in her biographies.

Differential diagnosis

MS and related disorders

MS is characterized by the dissemination in time and space of the lesions (plaques). It typically occurs in young adulthood, and most of the cases are relapsing-remitting MS (RRMS), while in 10–20% the clinical course is primary progressive (PPMS), without apparent relapses or remissions. Approximately 65% of the RRMS may transform its clinical course into the secondary progressive form (SPMS) after 15–20 years of onset [9].

Both Corona et al. [10] and Tierradentro-García et al. [11] assume that her case was RRMS that evolved into SPMS. Most of her early symptoms were, however, very short-lasting, and although many of them do meet the definition of relapse in that they continued for more than 24 h, we cannot identify indisputable major relapse episodes in her

early clinical stage. If her diagnosis is MS, PPMS will be more plausible.

Now in this article we would like to cast doubt on the diagnosis itself because of the following points. First, the pattern of her symptom progression seems ascending, not disseminated in space. Second, the symptoms appear steroid-dependent. Third, Uhthoff phenomenon might have been absent.

The ascending pattern of progression does not exclude MS by itself, but the probability of plaque accumulation with an ascending direction is presumed to be very low. Her early symptoms involved either or both of the upper and lower limbs indicating spinal cord lesions, and according to the biographies there were not a few episodes involving only the upper limbs (p. 360 [3], p. 364 [3], p. 398 [3], p. 166–7 [4]). The responsible lesion for the latter is difficult to localize except for the central portion of the cervical cord, a gray matter, not a principal target of MS.

She had had cortisone injections every other day (p. 202 [4]) and her clinical status appeared steroid-dependent, because “when she stopped taking them, she experienced further small relapses,” quickly (p. 256 [2], p. 410 [3]). In MS a meta-analysis shows that low to middle doses of corticosteroids (below 1 mg/kg/day of prednisolone equivalent dose) cannot prevent relapses [12], whereas high dose of corticosteroids is reported to be effective to prevent relapses in MS [13–15]. We have no information about the dose in her case, and although the effect of corticosteroids was at best temporary and there was no great impact on the progress of the disease (p. 410 [3]), it is unusual that her symptoms were steroid-dependent, and the diagnosis of MS should be laid under criticism.

Before the diagnosis, she struggled in vain to counter her disability with a long rehearsal before the concerts. Hot baths were counterproductive (p. 160 [4]). Furukawa discusses that she had experienced Uhthoff phenomenon, the worsening of symptoms by the elevation of body temperature, a characteristic feature of MS [16]. It may be true about the fatigue after hot baths, which all of us may have experienced, but a long exercise before the concert must have further aggravated her performance if Uhthoff phenomenon was positive, and she would have stopped this struggle as soon as she noticed its ineffectiveness. On the contrary, if she continued this struggle for some period of time, it is possible that her warming-up showed some effect no matter how small it was. In this case the demyelinating pathology is refuted rather than supported.

Acute disseminated encephalomyelitis (ADEM) is usually a monophasic disease unlike her case. Multiphasic disseminated encephalomyelitis (MDEM), the relapsing form of ADEM, resembles MS but its relapses are mostly fulminant. Repeated occurrence of mild transient episodes in her case precludes the possibility of MDEM. The neuromyelitis optica spectrum disorders and myelin oligodendrocyte glycoprotein antibody-associated disease are recently recognized disease entities distinct from MS, and corticosteroids reduce the risk of relapses, but there are no known progressive phenotypes [17]. Her clinical course was progressive and much more malignant than that expected in them.

Brain tumor or another space-occupying lesion

She had her skin moles excised in 1971, and neurofibromatosis or other neoplastic diseases affecting nervous tissue can be suspected. A single space-occupying mass within or adjacent to the central nervous system cannot, however, explain her limb-onset and eventually generalized symptoms, except when it was originally situated at the cervical spinal cord and later expanded to cause obstructive hydrocephalus. Slowly growing multiple intracranial and intrathecal tumors are difficult to rule out, but they cannot explain her ascending symptom progression.

Syringomyelia

Syringomyelia is a pathological cavity formation within the spinal cord. It may be primary or secondary, and in most cases it is associated with some underlying anomaly, exemplified by Chiari malformation and congenital anomaly of the brain, the spinal cord, or the cranio-cervical junction. Tumor, trauma, or hemorrhage of the spinal cord and the spinal adhesive arachnoiditis may also underlie the syrinx formation, although when tumor-related it is regarded as “tumor cyst” but not syringomyelia. She had had no past history of a heralding spinal cord damage or any major anomaly of the central nervous system, whereas Chiari malformation type I is a possible underlying anomaly in her case.

Chiari malformation is usually regarded as a congenital hindbrain anomaly and is classified into several types, among which type I with a caudal descent of cerebellar tonsils is the most common form. It is mostly benign [18] and often remains asymptomatic until young adulthood. It may be associated with syringomyelia in up to 80% [19], occasionally with the syrinx formation within the brainstem (syringobulbia) [20,21], and with obstructive hydrocephalus approximately in 10% of the cases [22]. Without CT or MRI it is difficult to make their objective diagnoses, and in pre-MRI era, multiple sclerosis was a common misdiagnosis of Chiari malformation in adults [23]. Our hypothesis is that all these pathologies had developed in her, initially with Chiari malformation type I and syringomyelia.

Her earliest symptoms, blurred vision and diplopia, may have been due to strabismus and nystagmus associated with underlying Chiari malformation [24]. In syringomyelia symptoms commonly develop in early adulthood and are characterized typically but not as a “sine qua non” by the dissociated sensory deficit; the loss of superficial sensation but preserved deep sensation. Cervical cord is most commonly affected, and at first only the upper limbs may be involved as was often seen in the early stage of her disease, although dissociated sensory deficit was not evident according to the biographies. When long spinal tracts are involved, the loss of deep sensation, paraparesis, or neurogenic bladder may occur, all of which were her symptoms. In syringobulbia damage of cranial nerves causes dysphagia and dysarthria, again as was the case in her. Her personality changes and cognitive decline in later years can be explained with progression of hydrocephalus. Bouncing of head in later years resembles that of the bobble-head doll syndrome in children, which is caused by the obstructive hydrocephalus [25]. Modest benefit of corticosteroids in her early years may have been obtained via temporary reduction of spinal cord swelling and edema (“presyrinx state”) occasionally preceding the rapid expansion of the syrinx.

Maybe an overstatement, but her skin moles may have been neurofibromas. A large clinical study disclosed that neurofibromatosis type 1 (NF1) was associated with Chiari malformation type I in 5% of the 500 cases [22]. Theoretically, not all but some of her symptoms may have been related to glioma(s) associated with NF1.

Neurodegenerative diseases

Amyotrophic lateral sclerosis is a motor neuron disease and objective sensory loss is usually absent, unlike her case. Spinocerebellar ataxia is discordant with her whole clinical course, particularly with sensory dominant symptoms of the limbs in her early years.

Other hereditary neurological diseases

Her father suffered from elderly-onset Parkinson’s disease (p. 276 [2]), and one of her distant relatives in the same generation had had multiple sclerosis (p. 318 [2]) but without detailed information. Other family history about neurological diseases is unremarkable. A mitochondrial disease includes a variety of clinical syndromes and is one of the differential diagnoses, but any distinct clinical entity does not meet her clinical course and symptoms. No laboratory data are available to support or refute the mitochondrial abnormality.

Systemic diseases

Her symptoms were mostly neurological and there were no apparent symptoms indicating damages of other organs, hence it is unlikely that her nervous system was offended by a systemic illness. No laboratory data are available in her biographies.

Infectious diseases

Neurosyphilis is unlikely because of the lack of symptoms associated with syphilis during the whole course of her disease. Progressive multifocal leukoencephalopathy progresses much faster than her case. HTLV-I associated myelopathy is a slowly progressive disease caused by the infection of the HTLV-I virus, endemic in some geographic regions not including western Europe. Brain may be involved, but symptoms typically start in the lower limbs and the principal focus of the disease continues to be the spinal cord.

Functional (Psychogenic) disorder

She had natural tendency of depression (p. 178 [4]) and had always had a fear that she had to pay recompense for her talent (p. 433 [3], p. 183 [4]), which may be reflected on her ominous statements about her tragic future (p. 50 [2], p. 324 [2]). Before diagnosis in 1973 her symptoms had been ascribed to depression (p. 380 [3]), unconscious resistance (p. 237 [2]), adolescent trauma (p. 239 [2]), mental stress (p. 244 [2]), or hysteria (p. 398 [3]). We have no reasonable information to explain to which extent her physical symptoms were psychological in origin, but some psychogenic overlay is suspected considering her mental collapse particularly in 1971. Her personality changes in her late years may be at least partially related to steroid psychosis because already in her earlier years she “tended to be euphoric rather than depressed” (p. 410 [3]) due to corticosteroids.

Discussion

Jacqueline du Pré presented with repeated episodes of limb numbness or weakness in her early stage of the disease, followed by brainstem symptoms, and eventually by cognitive and affective problems, but not by total intellectual degradation. Despite complaints of transient blurred or double vision there was no evidence for retrobulbar optic neuritis. It is uncertain whether recurrent cystitis had any relationship to her fatal disease. Her exhaustion and fatigability may have been due to her hectic private life and musical duties, in addition to her tendency of depression.

In modern medicine the diagnosis of MS is strongly dependent on MRI, which was unavailable in 1970's. Hence her diagnosis must have been made based on the clinical course and symptomatology. The clinical hallmark of MS is the dissemination in time and space. In her case, repetitive exacerbations are compatible with dissemination in time, but there appear to have been no clear-cut relapses in the early stage characterizing RRMS. Most of early episodes were brief and too obscure to pinpoint the responsible lesions, and later the exacerbations changed their form to staircase-like or relentless progression, apparently with an ascending direction. Thus further discussion is warranted about dissemination in space.

Her early symptoms were often confined only to the upper limbs, or only to the sensory symptoms without motor weakness. The most detailed description is about the episode at the rehearsal and concerts with Leonard Bernstein and the New York Philharmonic in February 1973 (p. 398 [3], p. 166–7 [4]). It is strange that she could perform on three concerts despite her serious trouble of her hands. One of the authors (KN), as a former amateur violinist who was a finalist in some domestic and international competitions in her adolescence, surmises that however well trained the player is, it is impossible to play any stringed instrument if either side of the upper limbs has lost its

sensation or motor strength and that the player cannot compensate the organic deficit with fortitude. Furthermore, concert reviews did not seem to point out her gait problem, which implies that her gait was normal or at least not prominently abnormal on the stage, supporting the assumption that her lower limbs were not much involved despite severe hand symptoms that made the last concert on the 27th cancelled.

How could she manage to perform on the cello despite serious sensory and motor deficits of her upper limbs however difficult it was? Furthermore, her lower limbs did not seem to be affected at least during the first three concerts. How can we explain this dissociation of deficits between the upper and lower limbs?

We have no information to answer the former question, but to the latter, there is one possible solution; this suspended pattern of deficits confined to the upper limbs typically indicates cervical syringomyelia.

Syringomyelia is a chronic progressive disease caused by the syrinx within the spinal cord. It often occurs in association with Chiari malformation type I and occasionally accompanied by obstructive hydrocephalus. The syrinx most often originates in the cervical cord and may extend upward and downward. In her case, repeated Valsalva maneuvers inevitably required during each performance might have extended the syrinx to the medulla oblongata (syringobulbia) by the “slosh mechanism” [26]. The symptoms of syringobulbia include headache, vertigo, dysarthria, trigeminal neuropathy, dysphagia, and diplopia, some of which were her symptoms. If obstructive hydrocephalus had developed in her case and it was the cause of her cognitive decline and affective symptoms, a single disease complex can explain her diverse but ascending symptomatology, and the dissemination in space is dismissed. Adjunctive evidence against MS is her apparent steroid-dependence in the early phase, which does not always exclude MS, but the reduction of focal swelling and edema of the spinal cord is a plausible explanation for the temporary benefit of corticosteroids only in the early years. More information is necessary about Uhthoff phenomenon in her case, although we doubt its presence.

We admit that multiple sclerosis is still a likely diagnosis, but her case is atypical and alternative interpretation is also possible. More information may be uncovered in the future, if it does not insult her relatives or people concerned. We imagine that modern diagnostic technology could have easily confirmed her disease and advanced medical and surgical techniques may have halted the symptom progression or greatly improved her functional outcome. She is still only a septuagenarian if alive today!

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

- [1] Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018;17:162–73.
- [2] du Pré H, du Pré P. Hilary and Jackie. The true story of two sisters who shared a passion, a madness and a man. New York: Ballantine Books; 1997.
- [3] Wilson E. Jacqueline du Pré. Her life, her music, her legend. New York: Arcade Publishing; 2013.
- [4] Easton C. Jacqueline du Pré. A biography. Da Capo Press; 2000.
- [5] New York Philharmonic. Leon Levy Digital Archives; 1973. Feb 22, 23, 24 / Subscription Season / Bernstein. https://archives.nyphil.org/index.php/artifact/2a54d286-9c24-4182-b015-525c17fa2e79-0.1?search-type=singleFilter&search-text=*du+Pré&search-dates-from=&search-dates-to= (accessed 17.09.2019).
- [6] Jacqueline du Pré's musical stories – Dukas, L. Mozart, Prokofiev, Saint-Saens [Compact Disc]. Australian Eloquence/DG 4800475; 2008.
- [7] Jacqueline du Pré – a celebration of her unique and enduring gift [DVD]. The Christopher Nupen Films, A07CND; 2007.
- [8] The New York Times. Jacqueline du Pré, noted cellist, is dead at 42; 1987. <https://www.nytimes.com/1987/10/20/obituaries/jacqueline-du-pre-noted-celist-is-dead-at-42.html> (accessed 17.09.2019).
- [9] Compston A, Coles A. Multiple sclerosis. *Lancet* 2008;372:1502–17.
- [10] Corona T, Poser C. Jacqueline Du Pré. Talent and disease. *Neurologia* 2004;19:85.

- [11] Tierradentro-García LO, Botero-Meneses JS, Talero-Gutiérrez C. The sound of Jacqueline du Pré: revisiting her medical and musical history. *Mult Scler J Exp Transl Clin* 2018;4. 2055217318775756.
- [12] Brusaferrri F, Candelise L. Steroids for multiple sclerosis and optic neuritis: a meta-analysis of randomized controlled clinical trials. *J Neurol* 2000;247:435–42.
- [13] Zivadinov R, Rudick RA, De Masi R, et al. Effects of IV methylprednisolone on brain atrophy in relapsing-remitting MS. *Neurology* 2001;57:1239–47.
- [14] Sorensen PS, Mellgren SI, Svenningsson A, et al. NORdic trial of oral Methylprednisolone as add-on therapy to Interferon beta-1a for treatment of relapsing-remitting Multiple Sclerosis (NORMIMS study): a randomised, placebo-controlled trial. *Lancet Neurol* 2009;8:519–29.
- [15] Ravnborg M, Sørensen PS, Andersson M, et al. Methylprednisolone in combination with interferon beta-1a for relapsing-remitting multiple sclerosis (MECOMBIN study): a multicentre, double-blind, randomised, placebo-controlled, parallel-group trial. *Lancet Neurol* 2010;9:672–80.
- [16] Furukawa T. Jacqueline du Pré and multiple sclerosis [Japanese]. *Neurol Med* 2018;89:638–40.
- [17] Juryńczyk M, Jacob A, Fujihara K, Palace J. Myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease: practical considerations. *Pract Neurol* 2019;19:187–95.
- [18] Langridge B, Phillips E, Choi D. Chiari malformation type 1: a systematic review of natural history and conservative management. *World Neurosurg* 2017;104:213–9.
- [19] Botelho RV, Bittencourt LR, Rotta JM, Tufik S. Polysomnographic respiratory findings in patients with Arnold-Chiari type I malformation and basilar invagination, with or without syringomyelia: preliminary report of a series of cases. *Neurosurg Rev* 2000;23:151–5.
- [20] Elster AD, Chen MY. Chiari I malformations: clinical and radiologic reappraisal. *Radiology* 1992;183:347–53.
- [21] Shen J, Shen J, Huang K, Wu Y, Pan J, Zhan R. Syringobulbia in patients with Chiari malformation type I: a systematic review. *Biomed Res Int* 2019;2019:4829102.
- [22] Tubbs RS, Beckman J, Naftel RP, et al. Institutional experience with 500 cases of surgically treated pediatric Chiari malformation type I. *J Neurosurg Pediatr* 2011;7:248–56.
- [23] Levy WJ, Mason L, Hahn JF. Chiari malformation presenting in adults: a surgical experience in 127 cases. *Neurosurgery* 1983;12:377–90.
- [24] Chapelle AC, Plant GT, Kaski D. Teaching Video NeuroImages: cerebellar esotropia: a pitfall in ophthalmology and neurology. *Neurology* 2019;93:e114–5.
- [25] Renne B, Rueckriegel S, Ramachandran S, Radic J, Steinbok P, Singhal A. Bobble-head doll syndrome: report of 2 cases and a review of the literature, with video documentation of the clinical phenomenon. *J Neurosurg Pediatr* 2018;21:236–46.
- [26] Williams B. Syringomyelia. *Neurosurg Clin N Am* 1990;1:653–85.