

TDP43 pathology in the brain, spinal cord, and dorsal root ganglia of a patient with FOSMN

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Abstract

Objective

To describe the histopathologic features of a case of facial-onset sensory and motor neuronopathy (FOSMN).

Methods

We describe a postmortem examination performed on a 54-year-old man with FOSMN associated with personality change.

Results

Postmortem examination revealed TAR DNA-binding protein (TDP) 43 proteinopathy with widespread distribution. TDP43 pathology was seen in the neurons and glial cells and was most pronounced in the subthalamic nucleus followed by the spinal cord, including dorsal root ganglia, brainstem, and other deep cerebral nuclei. In the medial temporal lobe, neocortex and subcortical hemispheric white matter TDP43 pathologic inclusions were very rare. In contrast to TDP43 pathologies associated with typical amyotrophic lateral sclerosis (ALS) or frontotemporal dementia (FTD)–TDP, in this case, there were more frequent TDP43-positive oligodendroglial, coiled body–like cytoplasmic inclusions than neuronal inclusions. Neuronal cytoplasmic TDP43 inclusions with globular and skein-like morphology were seen in both anterior horn cells and dorsal root ganglia. No β -amyloid, α -synuclein, or significant hyperphosphorylated tau pathology was seen.

Conclusion

This case provides further evidence that FOSMN is a neurodegenerative disease characterized by TDP43 pathology. Despite minimal cortical TDP43 pathology, the clinical features of the behavioral variant of FTD in this patient suggest that FOSMN may fall within or overlap with the FTD-ALS spectrum.

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Glossary

ALS = amyotrophic lateral sclerosis; **DRG** = dorsal root ganglia; **FOSMN** = facial-onset sensory and motor neuronopathy; **GCI** = oligodendroglial coiled body–like cytoplasmic inclusion; **NCI** = neuronal cytoplasmic inclusion; **TDP** = TAR DNA-binding protein.

Facial-onset sensory and motor neuronopathy (FOSMN) is a rare clinical syndrome characterized by asymmetric facial numbness or paresthesia, bulbar palsy, and facial weakness, which may progress to the upper limbs.¹ The FOSMN syndrome was first described in 2006, and since then, >40 cases have been described.^{2,3} Onset is typically in the fifth to seventh decade (but has been reported in patients as young as 7 years of age⁴), and the rate of progression can vary from months to decades.

The pathogenesis of FOSMN remains controversial. Initial reports described the presence of anti-ganglioside antibodies and response to immunotherapy,⁵ whereas others have described a progressive and terminal decline, resistant to immunotherapy and suggestive of bulbar-onset amyotrophic lateral sclerosis (ALS).^{3,6–8} Two of 3 postmortem studies of patients with FOSMN have revealed the presence of TAR DNA-binding protein (TDP) 43 inclusions in the brainstem nuclei and cervical motor neurons.^{3,7,8} In this article, we describe a patient with FOSMN and behavioral change in whom postmortem examination revealed frequent pathologic TDP43 inclusions in the deep cerebral nuclei, brainstem, and spinal cord and rarely in the medial temporal lobe, frontal cortex, and dorsal root ganglia (DRG).

Methods

Formalin-fixed, paraffin-embedded brain and spinal cord tissue was available from selected regions (table 1). The paraffin sections were cut at 5 μ m, mounted on glass slides, and stained with routine hematoxylin and eosin. Representative 5- μ m sections were immunostained for TDP43, β -amyloid, α -synuclein, hyperphosphorylated tau, p62, and CD68 with the following antibodies: TDP43 (2E2-D3, 1:3,000, Abcam, Cambridge, UK), β -amyloid (6F3D, 1:50, DAKO, Glostrup, Denmark), α -synuclein (KMS1, 1:50, Leica/Novocastra, Buffalo Grove, IL), AT8, (MN1020, 1:100, Invitrogen, Carlsbad, CA), p62 (3/P62LCK Ligand, 1:100, BD Transduction, East Rutherford, NJ), and CD68 (PG-M1, 1:100, DAKO), respectively. Immunostaining was performed on either a BondMax autostainer (Leica Microsystems, Wetzlar, Germany) or a Roche (Basel, Switzerland) Ventana Discovery automated staining platform following the manufacturer's guidelines, using biotinylated secondary antibodies and a horseradish peroxidase–conjugated streptavidin complex and diaminobenzidine as a chromogen. All immunostainings were carried with appropriate controls. Gliosis, microglial activity, and the density of TDP43 pathologic inclusions were scored semiquantitatively.

Data availability statement

All data relevant to this study are contained within the manuscript.

Results

A 54-year-old right-handed man presented with symptoms of facial numbness, dysarthria, and dysphagia and inappropriate behavior. Nine years previously, after a dental extraction, he developed numbness of the left upper lip that over 5 years spread to involve his tongue and left cheek and was associated with dysphagia and nasal regurgitation. A collateral history obtained from his wife reported that since the onset of the dysphagia, the patient's behavior had changed and he had difficulty maintaining his train of thought. There was no family history of neurodegenerative disease.

A Mini-Mental State Examination was normal; however, he was noted to have an inappropriate jocular manner. Clinical examination revealed a cachectic man. There was diminished light touch sensation in all territories of the trigeminal nerve and diminished pinprick sensation in the left mandibular territory. The corneal reflexes were absent. There was bilateral facial myokymia. The gag reflex was absent, and there was weakness of neck flexion, along with wasting and fasciculation of the tongue. In the upper limbs, there was wasting and weakness of the deltoids. There was no wasting, weakness, or sensory disturbance of the lower limbs. The knee and ankle reflexes were preserved, and the plantar responses were absent.

Nerve conduction studies performed 5 years after the onset of his symptoms revealed normal sensory and motor action potentials and conduction velocities in the upper and lower limbs (table 2). EMG demonstrated large individual motor units firing at high rates in a grossly reduced interference pattern, indicative of chronic denervation, in the sternocleidomastoid and orbicularis oculi. There was no evidence of acute denervation. Blink reflexes were absent bilaterally.

MRI scans of the brain and spine were normal. Fluorodeoxyglucose PET CT scan revealed an enlarged jugular lymph node that was subsequently biopsied and showed nonspecific reactive lymphoid hyperplasia. Duodenal biopsies were negative for Whipple disease. A lip biopsy was unremarkable. CSF examination was normal, including oligoclonal bands and Whipple PCR. Genetic testing for Kennedy disease, dentatorubral-pallidoluysian atrophy, and spinocerebellar ataxia types 1, 2, 3, 6, and 7 was negative. Routine blood tests were all normal.

Table 1 Available and analyzed brain and spinal cord regions

Region	Neuronal loss/gliosis	TDP43 and p62 NII	TDP43 and p62 NCI	TDP43 and p62 GCI	TDP43 and p62 DN long, thick	TDP43 and p62 DN short, thin
Dorsal root ganglion, level NOS	+	-	+	-	-	-
Anterior horn cells (lumbar)	+/-	-	+	++	-	++
Substantia gelatinosa (thoracolumbar)	+/-	-	-	+	-	-
White matter, spinal cord	NA	NA	NA	+	-	-
12th nucleus	+/-	-	-	++	-	+
10th nucleus	+/-	-	-	+	-	-
Medulla tegmentum (including fifth nucleus)	+/-	-	+	++	-	++
Inferior olivary nucleus	-	-	+	+	-	+
Pyramidal tract	NA	NA	NA	-	-	-
Substantia nigra	+	-	+	++	-	++
Red nucleus	-	-	-	++	-	+
Midbrain cerebral peduncle	-	NA	NA	+	-	+
Third nucleus	-	-	-	+	-	+
Midbrain tegmentum	-	NA	NA	++	-	+
Anterior hippocampus	-	-	-	CA1&4 +	-	-
Dentate gyrus	-	-	-	-	-	-
Parahippocampal gyrus	-	-	-	-	-	-
Amygdala	-	-	-	+	-	+
Cingulate gyrus	-	-	+	-	-	-
Putamen	-	-	+	++	-	+
Globus pallidus	-	-	+	++	-	+
Pencil fibres	NA	NA	NA	++	-	+
Thalamus	-	-	+	++	-	-
Subthalamic nucleus	+++	-	-	+++	-	+
Insular cortex	-	-	-	-	-	-
Neocortex, NOS	-	-	+	+	-	+
Subcortical white matter, NOS	-	NA	NA	+	-	+
Occipital lobe	-	-	-	-	-	-
Motor cortex	-	-	+	-	-	+
Betz cells	-	-	-	NA	NA	NA
Purkinje cells	+	-	-	-	-	-
Granule cells	-	-	-	-	-	-
Dentate nucleus	-	-	+	-	-	-
Cerebellar white matter	-	NA	NA	++	-	+

Abbreviations: DN = dystrophic neurites; GCI = glial cytoplasmic inclusions; NA = not applicable; NCI = neuronal cytoplasmic inclusions; NII = neuronal intranuclear inclusions; NOS = not otherwise specified; TDP43 = TAR DNA-binding protein 43; - = absent inclusions or no neuronal loss or no gliosis; +/- = no overt loss; +, ++, +++ = rare, moderate, frequent inclusions, respectively. Neuronal loss, gliosis, and TDP43-positive pathologic inclusions are scored semiquantitatively.

Table 2 Neurophysiologic studies

Sensory nerves	SAP, μ V	CV, m/s	Motor nerves	MCV, m/s	DML, ms	CMAP, mV
Right median	13	54	Right median (APB)	3.1	12.4	54
Right sural	21	48.5	Right ulnar (ADM)	2.5	10.4	54
			Right common peroneal	3.8	6.3	43
			Right tibial (AH)	5.3	9.0	59

Abbreviations: ADM = abductor digiti minimii; AH = abductor hallucis; APB = abductor pollicis brevis; CMAP = compound muscle action potential; CV = conduction velocity; DML = distal motor latency; MCV = motor conduction velocity; SAP = sensory action potential.

Formal neuropsychometry demonstrated a verbal IQ of 115 and performance IQ of 114, with average subtest scores except for arithmetic and picture completion, which were superior. Recognition memory tests were almost flawless (words 48 of 50, faces 50 of 50). Although he performed adequately on tests sensitive to frontal lobe dysfunction, he was noted to be inappropriately jocular during testing.

The patient was diagnosed with a progressive brainstem syndrome. In hindsight, the clinical syndrome is FOSMN, but this diagnosis had not been described at the time the patient presented. Because an inflammatory brainstem disorder remained a possibility, the patient was treated with a 3-month course of oral steroids, but his condition continued to deteriorate, and he was readmitted to hospital with an aspiration pneumonia. A percutaneous gastrostomy tube was inserted, but against medical advice, he continued to eat and drink, leading to a final episode of aspiration pneumonia, of which he died, 9 years after the onset of his symptoms.

Postmortem examination

Pathologic TDP43-positive inclusions were seen in the form of neuronal cytoplasmic inclusions (NCIs), oligodendroglial, coiled body–like cytoplasmic inclusions (GCIs), and dystrophic neurites (figure). GCIs and dystrophic neurites were more frequent than NCIs. TDP43 pathology was most prominent in the subthalamic nucleus, followed by the thalamus, putamen, and globus pallidus (other deep cerebral nuclei were not available for the assessment), brainstem, and spinal cord (table 1). NCIs with globular and skein-shaped morphology were seen in both motor (anterior horn cells) and sensory (dorsal root ganglion) neurons. In the neocortex, subcortical hemispheric white matter, anterior hippocampus, amygdala, and cingulate gyrus, TDP43 pathology was present but very rare. In the cerebellum, there were GCIs in the white matter and rare NCIs in the dentate nucleus but none in the cerebellar cortex (table 1). TDP43-positive inclusions also showed immunoreactivity for p62. There were no diagnostically specific p62 immunoreactive inclusions in the cerebellum or hippocampal dentate gyrus to suggest *C9ORF72* pathology or neuronal intranuclear inclusions characteristic of *VCP* or *p62* mutations. Microglial activity, highlighted with CD68 immunostaining, was most prominent in the subthalamic nucleus with comparably mild activation

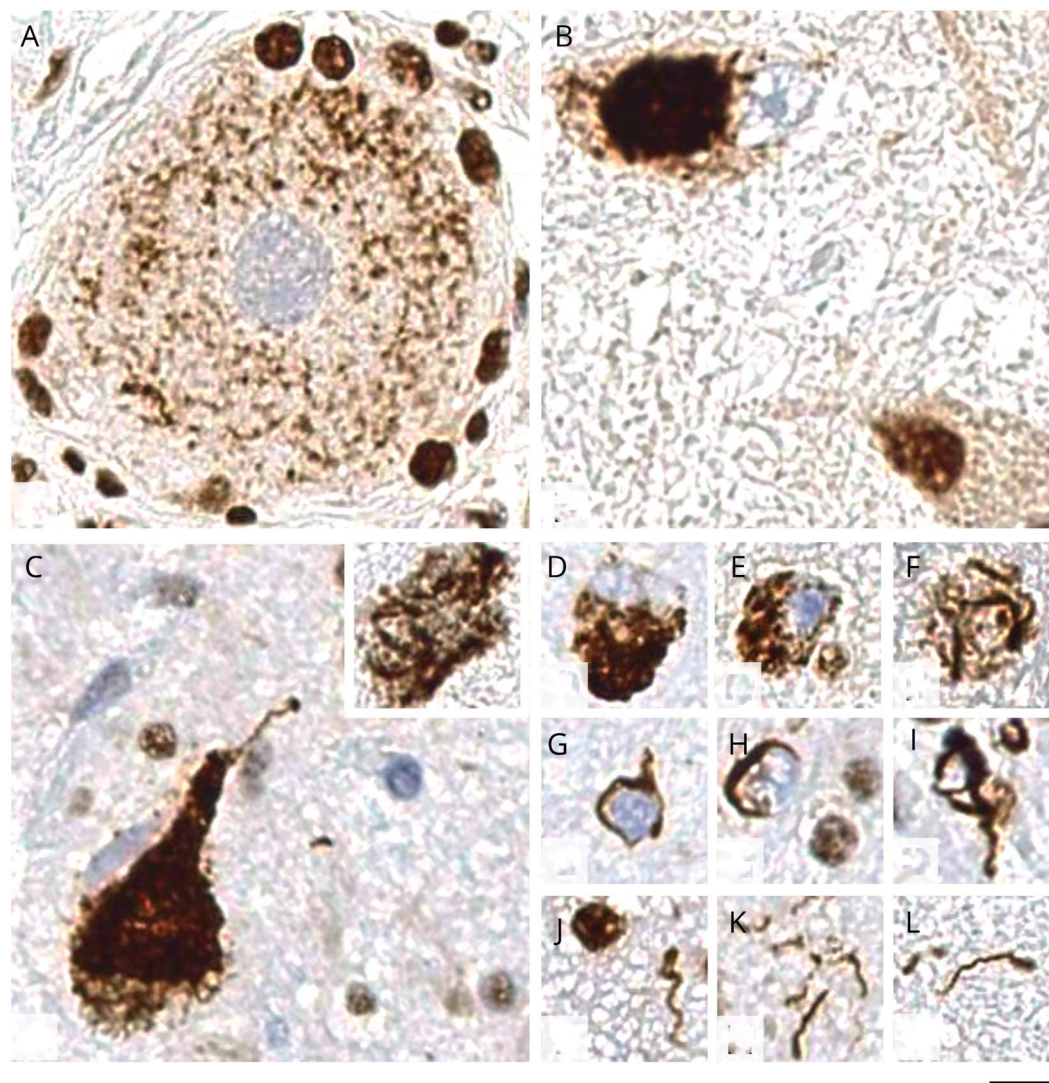
elsewhere, including the corticospinal tracts and anterior and posterior nerve roots in the spinal cord. No β -amyloid, α -synuclein, or significant hyperphosphorylated tau pathology was seen.

Discussion

In this report, we describe a case of FOSMN with personality change and a postmortem examination characterized by TDP43-positive inclusions in the cerebral cortex, brainstem, and spinal cord motor neurons and DRGs. Our findings corroborate the findings of 2 of 3 previous postmortem examinations of patients with FOSMN in which TDP43 inclusions were identified in the brainstem.^{3,7,8} This report provides further evidence that FOSMN may be considered a *forme fruste* of bulbar-onset ALS, a notion further supported by the behavioral change and TDP43 inclusions in the frontal cortex. We were unable to measure β -amyloid₄₂ and tau in the CSF because this assay was not available 15 year ago at the time of the patient's illness. It should also be noted that although the presence of TDP43 inclusions in the neocortex was unequivocal, they were infrequent.

The clinical syndrome of FOSMN was first described in 2006, several years after our patient's death.² Further histologic analysis was prompted by reports of TDP43 inclusions in postmortem tissue of patients with FOSMN.⁸ At the time of our patient's illness, mutations in *C9ORF72*, *FUS*, and *TARDBP* had not yet been discovered to cause ALS.

This report also describes the identification of TDP43 inclusions in the DRG of a patient with a sensory neuronopathy. This is an intriguing observation, and it is tempting to speculate that a neurodegenerative pathology, characterized by TDP43 inclusion in the DRG, may underlie a proportion of patchy asymmetric sensory neuronopathies that follow a progressive course and are resistant to immunosuppressive therapy.⁹ In further support of the pathogenicity of the TDP43 inclusions in the DRG is the recent report of a patient with an asymmetric patchy and progressive sensory and motor neuronopathy in whom a p.Arg382Pro missense mutation in *TARDBP* was discovered.¹⁰ This mutation is not present in the Exac database and has previously been described in



(A) Pathologic thread-like deposits in a neuron within dorsal root ganglion. (B) Globular cytoplasmic inclusion in the lumbar anterior horn motor neuron. (C) Large globular and skein-like (inset) cytoplasmic inclusions in pigmented neurons of the substantia nigra. (D–F) Various morphologies of neuronal cytoplasmic inclusions. (G–I) glial cytoplasmic inclusions, all of which show similar, coiled body-like morphology. (J–L) Appearances of dystrophic neurites, all of which are short and curved with no evidence of long neurites. All sections are immunostained with nonphosphorylated TAR DNA-binding protein 43 (TDP43) antibody, which detects normal nuclear TDP43 labeling and shows absent nuclear labeling in cells where there is TDP43 mislocalization from the nucleus to cytoplasm or cell processes. Scale bar: 10 μ m in panels A–L. FOSMN = facial-onset sensory and motor neuronopathy.

patients with ALS.¹¹ An additional distinctive feature seen in this patient and reported in the literature⁸ is the presence of widespread glial TDP43 pathology. TDP43-positive glial inclusions are also observed in both ALS and frontotemporal dementia–TDP, but to a much lesser extent, suggesting that there might be differences in molecular pathogenesis between FOSMN and ALS–frontotemporal dementia spectrum.

We describe TDP43 proteinopathy in a patient with FOSMN and personality change. The presence of TDP43 proteinopathy in the brain, spinal cord, and DRG and the discovery of a pathogenic *TDP-43* mutation in a patient with an asymmetric sensory and motor neuronopathy indicate that some sensory neuronopathies have a degenerative pathogenesis.

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Disclosure

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Appendix Authors

Name	Location	Role	Contribution
Alexander M. Rossor	UCL Institute of Neurology, UK	Author	Analysis of data and drafting of manuscript
Zane Jaunmuktane	UCL Institute of Neurology, UK	Author	Analysis and interpretation of data, drafting and revision of manuscript
Martin N. Rossor	UCL Institute of Neurology, UK	Author	Interpretation of data and revision of manuscript
Glen Hoti	UCL Institute of Neurology, UK	Author	Analysis of data and revision of manuscript
Mary M. Reilly	UCL Institute of Neurology, UK	Author	Design and conceptualization of the study, analysis of data, and revision of manuscript

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Disputes & Debates: Editors' Choice

Steven Galetta, MD, FAAN, Section Editor

Editors' note: ALS-specific cognitive and behavior changes associated with advancing disease stage in ALS

In "ALS-specific cognitive and behavior changes associated with advancing disease stage in ALS," Crockford et al. presented data that show that patients with ALS have impaired cognition and behavior and that these deficits worsen with increasing severity of disease. Raaphorst et al. question whether these changes are the result of frontotemporal dementia or nocturnal hypoventilation due to ALS-associated respiratory muscle weakness. They suggest that it would be helpful to have data on the number of stage 4 patients (patients with respiratory or nutritional insufficiency requiring intervention) who required noninvasive ventilation (NIV) and the extent of each subject's respiratory dysfunction. Abrahams and Crockford reply that 27.78% of stage 4 patients required NIV, but that there was no significant difference in cognition or behavior and requirement for NIV or lack thereof. However, they agree with Raaphorst et al. that given that respiratory dysfunction is a feature of late-stage ALS and memory impairment is associated with advanced-stage ALS, ventilatory support could potentially improve memory deficits in this population. They emphasize that further research on the relationship between respiratory dysfunction and cognition/behavior in ALS is required, as the current data on this topic come from a single small study.

Ariane Lewis, MD, and Steven Galetta, MD
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Reader response: ALS-specific cognitive and behavior changes associated with advancing disease stage in ALS

Joost Raaphorst (Amsterdam), Emma Beeldman (Amsterdam), Rosanne Govaarts (Amsterdam), Ben Schmand (Amsterdam), and Marianne de Visser (Amsterdam)
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We read the article by Crockford et al.¹ with great interest. Approximately 35% of patients with amyotrophic lateral sclerosis (ALS) have cognitive and behavioral changes, and 15% have frontotemporal dementia (FTD). The authors found increasing cognitive and behavioral impairment in patients with ALS, in relation to disease severity. We question the extent that these symptoms are ALS specific and reflect spread of the degenerative process in the prefrontal cortex, thus corroborating the link between ALS and FTD.

In ALS, respiratory muscle weakness (e.g., a vital capacity [VC] of 60%–80% of predicted) is associated with cognitive deficits (letter fluency and verbal memory), which improve by noninvasive ventilation (NIV).^{2,3} Behavioral impairment (apathy and hallucinations) may also be due to nocturnal hypoventilation.⁴ Patients in King's clinical stages 1–3 may already have some degree of respiratory involvement (e.g., a VC between 60%–80% without complaints of hypoventilation) associated with cognitive and behavioral impairment.

Author disclosures are available upon request (journal@neurology.org).

To appreciate more fully the important findings, it would be helpful if the authors present relevant data on respiratory assessments for each subgroup and their relation to cognitive and behavioral data. In addition, the proportion of King's stage 4 patients on NIV, if any, may be of interest.⁵

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Author response: ALS-specific cognitive and behavior changes associated with advancing disease stage in ALS

Sharon Abrahams (Edinburgh) and Chris Crockford (Edinburgh)
Neurology® 2019;93:86. doi:10.1212/WNL.00000000000007760

We thank Raaphorst et al. for the comment on our article.¹ We acknowledged the possible role of respiratory functioning in both the discussion and analysis of data without stage 4 patients; however, 27.78% (n = 15) of stage 4 patients in this study were on noninvasive ventilation (NIV) at the time of testing for at least 2 weeks. No substantial differences were found in any cognitive or behavioral domain between NIV and non-NIV stage 4 patients.

Few studies examine, in depth, the effect of respiratory dysfunction on cognition/behavior in amyotrophic lateral sclerosis (ALS). Moreover, the evidence that NIV ameliorates neuropsychological dysfunction is based on a single small study (n = 9), which found improved functioning in 2 of 6 memory measures, and not on verbal fluency.² The effect of respiratory dysfunction on cognition/behavior is not properly understood, and there is little evidence that this potential effect is transient.

Although we acknowledge the possible moderating role that respiratory insufficiency may play in cognitive dysfunction in ALS, this is not the sole driver of our results.¹ However, this highlights an important avenue for further research.

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Editors' note: To harvest?: A reality-based ethical dilemma and fictional dialogue

In the humanities section article “To harvest?: A reality-based ethical dilemma and fictional dialogue,” Drs. Smith and Riggs debate the ethics of harvesting a patient’s organs if their surrogate wants the organs donated but reports that the patient did not want to be an organ donor and then later revokes the comment about the patient not wanting to be a donor. They question whether the surrogate’s willingness to consent should override the possibility that the patient previously dissented and whether a statement made in passing that an individual does not want to be an organ donor represents informed dissent. Dr. Sethi notes that it is challenging to distinguish between uninformed and informed dissent when one cannot speak directly to the individual involved to ascertain whether they were competent and knowledgeable at the time of the dissent. However, he proposes that it may be helpful to interview the patient’s other family members about the issue of dissent. Drs. Smith and Riggs voice appreciation for Dr. Sethi’s thoughtful response and comment that it is helpful to contemplate ethical controversies in a hypothetical context to be better prepared to address them in real life.

Ariane Lewis, MD, and Steven Galetta, MD
Neurology® 2019;93:87. doi:10.1212/WNL.0000000000007763

Reader response: To harvest?: A reality-based ethical dilemma and fictional dialogue

Nitin K. Sethi (New York)
Neurology® 2019;93:87. doi:10.1212/WNL.0000000000007764

I read with rapt attention the reality-based ethical dilemma and fictional dialogue on organ harvesting after cardiac death by Drs. Smith and Riggs.¹ For informed consent to be truly informed, the information provided to the patient is a necessary and obligatory premise.² One may argue that it also depends on the competence and knowledge of the physician or the person providing the information to the patient. Informed dissent too has to meet the above prerequisites. In the authors’ fictional case,¹ it is impossible to determine the quality of the consent or dissent. The mother and close family members should be interviewed in depth in an attempt to ascertain this information. So, will I let the organs be harvested or not? To that question, I would answer, “No.”

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Author response: To harvest?: A reality-based ethical dilemma and fictional dialogue

Matthew S. Smith (Morgantown, WV) and Jack E. Riggs (Morgantown, WV)
Neurology® 2019;93:88. doi:10.1212/WNL.00000000000007765

We appreciate the rapt attention that our piece¹ evoked in Dr. Sethi. That is exactly the response we were hoping for in readers. When faced with these kinds of ethical dilemmas, one always wishes for more information. Ultimately, however, in these difficult situations, some decision and course of action (right or wrong) will occur. It is far better to have at least contemplated these issues beforehand, rather than only after one finds him/herself immersed in such issues.

1. Smith MS, Riggs JE. To harvest?: a reality-based ethical dilemma and fictional dialogue. *Neurology* 2018;91:666–667.

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CORRECTIONS

TDP43 pathology in the brain, spinal cord, and dorsal root ganglia of a patient with FOSMN

Neurology® 2019;93:88. doi:10.1212/WNL.00000000000007291

In the article “TDP43 pathology in the brain, spinal cord, and dorsal root ganglia of a patient with FOSMN” by Rossor et al.,¹ first published online January 30, 2019, the headings for table 2 should read “MCV, m/s” and “DML, ms.” The authors regret the errors.

Reference

1. Rossor AM, Jaunmuktane Z, Rossor MN, Hoti G, Reilly MM. TDP43 pathology in the brain, spinal cord, and dorsal root ganglia of a patient with FOSMN. *Neurology* 2019;92:e951–e956.

Journal Club: Florbetapir imaging in cerebral amyloid angiopathy-related hemorrhages

Neurology® 2019;93:88. doi:10.1212/WNL.00000000000007523

In the article “Journal Club: Florbetapir imaging in cerebral amyloid angiopathy-related hemorrhages” by Charidimou et al.,¹ the following reference should have been included, detailing a study by Dr. Nicolas Raposo et al.:

Raposo N, Planton M, Péran P, et al. Florbetapir imaging in cerebral amyloid angiopathy-related hemorrhages. *Neurology* 2017;89:697–704.

The authors regret the error.

Reference

1. Charidimou A, Giese AK, Pasi M, et al. Journal Club: Florbetapir imaging in cerebral amyloid angiopathy-related hemorrhages. *Neurology* 2018;91:574–577.