Clinical value of 2-deoxy-[¹⁸F]fluoro-D-glucose positron emission tomography in patients with cervical spondylotic myelopathy

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Cervical spondylotic myelopathy (CSM) is one of the most common spinal cord disorders in the elderly. It is usually diagnosed by MRI, but in a significant number of patients the clinical course of CSM does not correlate with the extent of the spinal cord compression. Recent studies have suggested that a distinct metabolic pattern of the cervical cord, as assessed by PET with 2-deoxy-[¹⁸F]fluoro-D-glucose (¹⁸F-FDG) may predict a patient's clinical outcome after decompressive surgery for cervical spine stenosis. The authors provide an overview of the recent literature regarding the value of PET with ¹⁸F-FDG of the cervical cord in patients with CSM, paying attention to prognostic aspects and the potential role of inflammatory processes in the acute phase of the disease.
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KEY WORDS • degenerative cervical spinal stenosis • glucose hypermetabolism •
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CERVICAL spondylotic myelopathy is one of the most common spinal cord disorders in people older than 55 years.²¹ Chronic degenerative changes of the vertebral disc, the intraspinal ligaments, and the adjacent bony structures of the vertebrae are normal aging processes of the cervical spine. Dislocated disc material, thickened yellow ligaments, slowly growing osteophytes, and spinal instability can lead to stenosis of the cervical spinal canal with mechanic compression and dysfunction of the cervical spinal cord (cervical myelopathy).

Constant compression of the cervical spinal cord at the level of stenosis and repetitive microtrauma during neck movement may lead to structural tissue damage. Atrophy and neuronal loss in the gray matter and demyelination in the white matter have been demonstrated in biomechanical and autopsy studies.^{20,23}

The diagnosis of a CSM is based on radiological and clinical findings. Typically, a degenerative cervical spine stenosis with compression of the cervical spinal cord and a cervical myelopathy with neurological deficits are present. Cervical myelopathy is usually a slowly progressive process taking place over years with phases of acute clinical deterioration, phases of partial spontaneous recovery, and phases of chronically persistent deficits. Symptoms often develop insidiously and are characterized by neck stiffness, arm pain, numbness in the hands, and weakness of the hands and legs. It can finally lead to complete paralysis of all neurological functions below the level of stenosis.^{1,5} To quantify the clinical impairment, the functional status in patients with CSM is usually assessed by the JOA scoring system.

Cervical Spondylotic Myelopathy

Morphological Imaging of CSM Using MRI

Clinically, CSM is usually visualized using MRI,

Abbreviations used in this paper: CSM = cervical spondylotic myelopathy; JOA = Japanese Orthopaedic Association; ¹⁸F-FDG = 2-deoxy-[¹⁸F]fluoro-D-glucose.

which offers an excellent visualization of the morphological aspects with high spatial resolution. The detection of stenosis, effacement of the subarachnoid space, spinal cord compression, and an intramedullary hyperintensity on T2-weighted images (the “myelopathy sign”) are the essential findings.

However, the presence of these radiological features in patients with CSM does not always result in clinical symptoms (see Fig. 1B).¹⁹ Structural MRI defines the location and extent of cervical spine stenosis but may not reflect the complexity of this morphologically stable but clinically dynamic disease with variable courses even in asymptomatic patients. It is unclear how patients with cervical spine stenosis, obvious spinal cord compression, and MRI-documented myelopathy sign switch from a clinical inactive (asymptomatic) phase to one of symptomatic CSM.

Cervical spine stenosis and compression of the cervical cord are the primary causes of CSM. Thus, decompressive surgery appears to be the treatment of choice to improve the patients’ symptoms and to prevent further clinical deterioration. Standard microsurgical anterior decompression and cage fusion or posterior decompression with eventual instrumentation placement is routinely performed. Despite excellent neurosurgical results regarding the mechanical decompression of the cervical spinal cord, which can be visualized on postoperative MRI, patients’ outcomes are variable and unpredictable. Neither clinical symptoms nor postsurgical outcome correlates with the morphological aspects of CSM as assessed by structural MRI.^{13,18,25,35}

To date, our knowledge of what brings about recovery, even without decompressive surgery to resolve the cause of compression, is limited. Recently, there has been

FIG. 1. Morphological and metabolic images in CSM in different clinical phases of the disease. **A:** Healthy control patient (JOA score of 17) without stenosis in MRI (A₁). The PET scan shows a linear homogeneous FDG uptake (A₂) along the complete cervical cord (“normometabolism”). **B:** Patient with incidental finding of radiological myelopathy. The T2-weighted MR image (B₁) shows a stenosis with cord compression and an intramedullary hyperintensity (arrow). Clinically there were no symptoms of myelopathy (JOA score of 17). The corresponding FDG PET (B₂) demonstrates a homogeneous glucose uptake (normometabolism) identical to healthy controls (A₂). **C–E:** Three patients with a clinically acute onset of progressive myelopathy symptoms (JOA score < 12) within the last 6 months. The MR images (C₁, D₁, and E₁) show, morphologically, the typical degenerative stenosis with cord compression and intramedullary hyperintensity (arrow). The corresponding ¹⁸F-FDG PET scans (C₂, D₂, and E₂) reveal an increased “peak” uptake of glucose (local hypermetabolism) at the individual level of stenosis. **F and G:** Two patients with clinically chronic myelopathy and stable symptoms (JOA score < 12) for at least 12 months. The MR images (F₁ and G₁) show, morphologically, typical degenerative stenosis with cord compression and intramedullary hyperintensity (arrow). The corresponding FDG PET scans (F₂ and G₂) show a poststenotic decrease of glucose uptake (hypometabolism). There is no “peak” uptake at the individual level of the stenosis.

Cervical spondylotic myelopathy and FDG PET

discussion of an inflammatory response of the chronically compressed cord.^{3,4,42}

Since morphological aspects of CSM visualized on MRI have no predictive value regarding the spontaneous clinical course and outcome after surgical decompression,^{13,18,25,34} ¹⁸F-FDG PET scanning has been evaluated as a tool to investigate the functional and metabolic changes in CSM.

¹⁸F-FDG PET Imaging in Patients With CSM

Metabolic evaluation of spinal cord pathologies using ¹⁸F-FDG PET has been performed for more than 25 years, especially in cases of neoplastic diseases^{8,16,24,26,27,29,32,40} but also in a variety of cases involving benign inflammatory intraspinal lesions such as infections,¹⁷ tophaceous gout,³³ and neurosarcoidosis.^{10,31} In all of these space-occupying and compressive lesions, ¹⁸F-FDG PET has been used to differentiate between benign and malignant pathologies or to monitor biological activity. For the most part, all malignant entities like spinal metastasis and inflammatory diseases like neurosarcoidosis are characterized by an increased glucose uptake. Furthermore, ¹⁸F-FDG PET has also been evaluated in patients with radiation-induced myelopathy. Increased glucose uptake has been observed within the areas of demyelination, and, furthermore, the glucose metabolism decreased correspondingly to clinical recovery during corticosteroid treatment.^{7,11,12,38} It was assumed that regional hypermetabolism in radiation-related myelopathy is caused by reparative processes.

In contrast to inflammatory and neoplastic disorders of the cervical spine, myelopathy caused by degenerative compression (that is, CSM) is a much more frequent clinical problem, especially in our aging society. To assess the metabolic aspects of compressive myelopathy, the glucose metabolism of the cervical spinal cord has been evaluated using ¹⁸F-FDG PET examinations.^{14,15,36,37,39} An overview of the different patterns of physiological and pathological glucose utilization in ¹⁸F-FDG PET is illustrated in Fig. 1.

Physiological Glucose Uptake in Healthy Controls

Anatomical visualization and glucose utilization in the uncompressed cervical spinal cord of healthy adults has been described previously. The pattern of physiological ¹⁸F-FDG uptake is characterized by a nearly homogeneous linear glucose uptake along the entire cervical spinal cord (Fig. 1A), with a slight decrease from the craniocervical to the cervicothoracic junction.^{8,9,14,15,22,28} A higher uptake at C-1 is observed in the majority of individuals and seems to be related to a spillover from the high glucose uptake of the lower brainstem.

Physiological Glucose Utilization in Asymptomatic Patients With MRI-Documented Myelopathy Sign

Identical to healthy individuals without spinal canal stenosis (Fig. 1A), asymptomatic patients with an incidental finding of cervical spinal canal stenosis, cord compression, and MRI-documented myelopathy sign may exhibit the same homogeneous linear glucose uptake in the whole cervical spinal cord (Fig. 1B). Despite the cervical cord compression, the patients' metabolic status remains

unaffected and the patients show no clinical symptoms of myelopathy.

Pathological Glucose Utilization in Symptomatic Patients With CSM

The first studies using ¹⁸F-FDG PET in small inhomogeneous groups of patients suffering from symptomatic compressive cervical myelopathy reported either a global reduction or global increase of ¹⁸F-FDG uptake across the entire spinal cord independent of the level of stenosis.^{2,36,39} This is surprising since compressive myelopathy is morphologically a local phenomenon on MRI and the neurological impairment, such as sensory and motor deficits, is predominantly related to the segments at and below the level of stenosis. Therefore, a local metabolic reaction of the damaged cervical spinal cord at and/or below the level of the cord compression should be expected instead of global changes in ¹⁸F-FDG uptake in the entire cervical cord.

Subsequent studies in larger patients groups have used more strict inclusion criteria, and the results suggest that monosegmental local compressive myelopathy on MRI corresponds to local—and not global—alterations in the glucose metabolism of the cervical cord, with strict relation to the individual level of stenosis (Fig. 1C–G).^{14,15,37} This may indicate that the alteration of glucose uptake is restricted to the neural tissue at the level of stenosis and distal to the mechanical compression and does not influence the entire cervical spinal cord.

Different patterns of pathological ¹⁸F-FDG uptake in patients with CSM have been observed, and the pattern may be specific for the different clinical phases of symptomatic CSM. The early myelopathy phase with acute onset of clinical deterioration is characterized by a focal hypermetabolism at the level of stenosis, while the late, more chronic myelopathy phase with persistent deficits exhibits a poststenotic hypometabolism.^{14,15,37}

Glucose Hypermetabolism at the Level of Stenosis

Patients in the acute-onset phase of symptomatic CSM and also patients with chronic-stable myelopathy and new-onset symptoms exhibit a focally increased ¹⁸F-FDG uptake at precisely the individual level of their stenosis and cord compression (Fig. 1C–E).^{14,37}

Decompressive surgery during the phase when hypermetabolism is present at the level of stenosis results in a good clinical recovery and favorable outcome with significant improvement of functional JOA scores.¹⁴ This suggests that the hypermetabolism at the stenotic level represents a condition with functionally damaged spinal cord that is potentially reversible.

Poststenotic Glucose Hypometabolism

With ongoing symptomatic CSM, the disorder's clinical activity may slow down and convert to a chronic phase of CSM. In this phase of myelopathy, the metabolic pattern may change; the initial focally increased glucose metabolism at the level of cervical cord compression vanishes and a poststenotic glucose hypometabolism occurs (Fig. 1F and G).^{14,15} The observed metabolic impairment

below the stenotic level accords with the clinical finding that permanent sensorimotor deficits affect only the dermatomes and muscles of the levels below the stenosis and cervical spinal cord compression.

Recent findings suggest that decompressive surgery during the phase of poststenotic hypometabolism results in a poor recovery and unfavorable outcome in which there is low to absent improvement of the functional JOA score.¹⁴ This suggests that the poststenotic hypometabolism represents a condition that involves an irreversibly damaged spinal cord.

Role of Compression-Induced Inflammation in CSM

Neuroinflammation has been suggested to play a key role in the pathophysiology of patients with CSM. Stirling and colleagues identified minocycline as a promising drug to reduce oligodendrocyte apoptosis in an animal model of acute cervical spinal cord injury.³⁴ Nobel and coworkers demonstrated that the administration of matrix metalloproteinase-9 inhibitor reduces tissue damage in an animal model of acute cervical spinal cord injury.³⁰

Despite several similarities between acute cervical spinal cord injury and CSM, CSM's slow progressive conditions seem to be unique. Thus, Yu et al.⁴² examined molecular changes in postmortem human spinal cord tissue from patients with CSM. They demonstrated that an innate immune response may lead to neuronal and oligodendroglial death, which was mediated by Fas and Fas ligands. After transforming this knowledge to an animal model of CSM, they furthermore have shown that blocking Fas by repeated injection of Fas ligand-neutralizing antibody improves locomotion in comparison with control animals.

On the basis of the experiences with other neuroinflammatory diseases (for example, multiple sclerosis), it is supposed that treatment with corticosteroids may suppress the influx of inflammatory cells and subsequently the epiphenomenon of hypermetabolism in the compressed cervical spinal cord. From findings in animal models it is known that increased ¹⁸F-FDG uptake occurs in inflammatory tissue,⁴¹ and both the invasion of inflammatory cells and the subsequently increasing ¹⁸F-FDG uptake can be successfully suppressed by administration of corticosteroids.⁶ Those findings provide a rationale for neuroprotective strategies in addition to treatment by the usual procedure of decompressive surgery. On the basis of these findings and other preclinical pharmacological treatment results, it has to be assumed then that antiinflammatory drugs like corticosteroids also may suppress the influx of inflammatory cells (for example, macrophages) as they do in other neuroinflammatory diseases (for example, multiple sclerosis).

A compression-induced inflammation of the cervical cord with infiltration of macrophages might be implicated in the acute onset of myelopathy symptoms and clinical deterioration. In the course of CSM, the initial clinical progression slows down, and symptoms may stabilize or even partially improve despite persisting stenosis and cervical cord compression. In patients with CSM in this phase of the disease, an inconspicuous ¹⁸F-FDG uptake is shown at the individual level of stenosis and cord com-

pression, and a decrease of ¹⁸F-FDG uptake is present below the stenotic level (Fig. 1F and G). It is tempting to speculate that neuroinflammation is a self-limiting process and, in this late phase of myelopathy, the compression-induced inflammatory reactions are completed and a structural damage of the cervical cord tissue remains.

Clinical Outcome and Metabolic Changes After Antiinflammatory Corticosteroid Treatment

In a recent study (Floeth et al., unpublished data), we tested the hypothesis of an inflammatory component in CSM. We analyzed the glucose metabolism in 2 patients with symptomatic CSM who refused to undergo surgical decompression of the stenosis. Both patients were clinically in the acute-progressive phase of their myelopathy, and, accordingly, PET scanning showed increased ¹⁸F-FDG uptake at individual level of stenosis. A high dose of oral corticosteroid therapy (cumulative dose of 42 mg dexamethasone over 8 days) was administered, which led to a reduction of the increased ¹⁸F-FDG uptake in the spinal cord to normal levels (Fig. 2B). This immediate effect of corticosteroid administration on ¹⁸F-FDG uptake in the spinal cord appeared to be similar to that observed after surgical decompression (Fig. 2A). Both patients made a slight clinical improvement, but this partial clinical recovery only lasted for a few weeks, when myelopathy symptoms worsened. Second-line surgical decompression resulted (Fig. 2B₃) in a good and stable clinical improvement in both patients.

These observations support the hypothesis that invasion of inflammatory cells (that is, macrophages), with their ability for clearance of cellular debris, and apoptotic cells contributes to the increased ¹⁸F-FDG uptake in an early hypermetabolic phase of cervical myelopathy, and steroid medication may be able to suppress this process of neuroinflammation (Fig. 2B).

Conclusions

The current literature suggests that metabolic imaging using FDG PET may play an important role in the management of patients with CSM. A hypermetabolism in the cervical spinal cord at the level of stenosis, as indicated by an increased ¹⁸F-FDG uptake, seems to be a marker for a potentially reversible phase of a compression-induced cervical myelopathy. The presence of this metabolic pattern appears to reflect the time frame when decompressive surgery can lead to substantial clinical improvement. Effective treatment of CSM must address the causative primary noxae of the cord compression within the stenosis, and there is no alternative to decompressive surgery (Fig. 2A). A substantial clinical improvement or even complete resolution of myelopathy symptoms can be achieved best within the initial acute progressive phase. The presence of temporary local hypermetabolism seen on ¹⁸F-FDG PET scans in this initial phase of myelopathy appears to reflect an acute inflammatory process, with a predominantly functional impairment of the neuronal tissue, and represents the phase of potentially reversible symptomatic CSM.

The focal hypermetabolism at the level of stenosis ap-

Fig. 2. Morphological and metabolic images in CSM before and after treatment. **A:** Effects of surgical decompression in a patient with acute onset of progressive myelopathy symptoms (JOA score of 9). The T2-weighted MR image (A₁) shows stenosis with cord compression and a faint intramedullary hyperintensity at the level C3–4 (arrow). The corresponding FDG PET scan (A₂) shows an increased glucose uptake at the level of stenosis (arrow) and a poststenotic decrease of glucose metabolism. Anterior decompression and fusion was performed, and the patient's symptoms improved considerably (JOA score of 15) within 1 year. The control MR image (A₁ post-OP) shows decompression of the cord and persistent intramedullary hyperintensity at the level of the former stenosis (arrow). In contrast, the corresponding control FDG PET scan (A₂ post-OP) indicates a complete decrease in the peak uptake of glucose at the level of the former stenosis and a normalized poststenotic uptake. **B:** Effects of antiinflammatory corticosteroid treatment in a patient with acute onset of progressive myelopathy symptoms (JOA score of 15). The MR image (B₁) shows CSM at the level C5–6 (arrow). The corresponding FDG PET scan (B₂) demonstrates a focally increased glucose uptake at the level of stenosis (arrow). The patient refused surgery, oral corticosteroid treatment was started, and myelopathy symptoms improved slightly (JOA score of 16). One day after steroid treatment, the control the MR image (B₁ post-steroids) is unchanged while the control FDG PET scan (B₂ post-steroids) shows a complete regression of the focally increased glucose uptake (arrow). Two months after steroid treatment, symptoms worsened again (JOA score of 14), and the patient underwent anterior decompression and fusion to treat the stenosis. Clinically the patient recovered completely (JOA score of 17). The postoperative control MR image (B₃ post-OP) demonstrates sufficient decompression of the cervical cord and the typical persistence of the intramedullary hyperintensity.

pears to be caused by a compression-induced inflammatory response that involves intramedullary infiltration of glucose-consuming macrophages. This hypothesis could be substantiated in recent experimental studies and provides a rationale for antiinflammatory medical treatment, with, for example, corticosteroids. Initial therapeutic trials with corticosteroids in single patients with acute CSM induced a decrease of local FDG uptake and improved clinical symptoms, which confirmed this hypothesis.

Thus, suppression of the compression-induced neuroinflammation using corticosteroids can improve clinical activity in acute CSM. Steroid treatment, however, does not eliminate the cause of the disease, and the clinical effect is only temporary. Nevertheless, this time interval can be used to prepare the patient for surgery. The pretreatment of neuroinflammation with corticosteroids stabilizes or improves the clinical status and offers some

time for decision making and preparation of the subsequent definitive treatment of the primary noxae of spinal cord compression by surgery.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Eicker, Floeth. Acquisition of data: Stoffels. Analysis and interpretation of data: Eicker, Stoffels, Floeth. Drafting the article: Eicker. Critically revising the article: Langen, Galldiks, Floeth. Reviewed submitted version of manuscript: Langen, Galldiks, Herdmann, Steiger, Floeth. Approved the final version of the manuscript on behalf of all authors: Eicker.

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