Future NEUROLOGY

EDITORIAL

From pneumomyelography to cord tractography: historical perspectives on spinal imaging



"Despite recent developments, an urgent and unmet need persists for sensitive spinal measures."

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Quantitative spinal cord imaging is one of the least explored frontiers of neuroradiology. While high resolution spinal cord imaging remains notoriously challenging, unprecedented technical advances have taken place in recent years foretelling exciting new clinical applications. The small cross-sectional area of the human cord, respiratory effects, cardiac pulsation and cerebrospinal fluid circulation are just some of the physiological factors making high quality spinal imaging significantly more difficult than brain imaging. Despite the anatomical and technical challenges, several MRI techniques previously only used in brain imaging, such as functional MRI and tractography, have recently been adapted to spinal applications.

Historically, spinal imaging has consistently lagged behind cerebral imaging. Vertebral x-rays dominated the early years of spinal radiography and emerging single-plane methods in the 1930s, such as tomography or planigraphy, only offered limited additional value in characterizing osseous lesions. It was not until the development of contrast-enhanced techniques that the outline of the cord was successfully visualized. Pneumomyelography, myelography, discography, spinal angiograms and computed tomography myelography are just some of the pre-MRI methods which have been successfully utilized to visualize soft tissue structures in the spinal canal. The diagnostic value, ingenuity and elegance of these techniques are remarkable given the technological constraints of the pre-MRI era. All of these techniques were invariably invasive and relied heavily on the dexterity of neuroradiologists. Despite their limitations, the incessant optimization of these methods epitomizes the timeless drive to characterize pathology *in vivo*, either as part of a pre-surgical assessment or in an effort to elucidate unexplained neurological symptoms. At a time when specific spinal tracts can be evaluated with tractography, metabolic information gained from magnetic resonance spectroscopy (MRS), and spinal functional MRI captures segmental activation, a historical perspective serves as a reminder of the relentless technological advances.

KEYWORDS
• biomarker • MRI
• neurodegeneration
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The advent & development of myelography

In Walter Dandy's original description of pneumoencephalography in 1919 there is a brief mention of visualizing the spinal cord contour following air injection [1]. In 1921 Hans Christian Jacobaeus and Sofus Widero proposed the use of pneumomyelography to diagnose spinal cord tumors [2]. The first contrast myleography is reported by Sicard and Forestier in 1922 [3]. Their use of iodized poppy seed oil (Lipiodol®) was originally intended for intramuscular and epidural injections for sciatica until the accidental injection of Lipiodol intrathecally serendipitously outlined the spinal cord under fluoroscopy [4]. Following the success of lumbar myelography, Sicard and Forestier began injecting Lipiodol by occipital cisterna magna puncture. In addition to cisternal puncture, high cervical punctures at C1-C2 were also routinely performed for both gas and contrast myelography [5]. Gas myelography and iodinated oil contrasts were gradually replaced by Iophendylate in the 1940s and subsequently by water soluble noniodinated contrast agents in the 1960s. From the late 1970s CT myelography became the standard procedure to image acute spinal pathologies. Despite the widespread availability of MRI, CT myelography is far from obsolete. In patients with pacemakers, spinal rods, screws and wires, CT myelography remains an invaluable diagnostic tool. While the first cerebral angiography was reported in 1927 [6], the first spinal angiography was not performed until 1966 and it is not until the advent of subtraction techniques in the late 1960s that vascular malformations were reliably visualized. The first description of discography was published by Swedish radiologist, Lindblom in 1948. Discographies were initially performed at a lumbar level from a posterior, midline transdural approach, slowly perfected into a posterolateral technique applicable to thoracic and cervical regions [7].

Current practice: methods, challenges & limitations

In current clinical practice, spinal MRI is the gold standard imaging modality in trauma, acute myelopathies, demyelination, suspected radiculopathy, lower back pain, and for detecting vascular malformations, tumors, syringomyelia and congenital malformations. While spinal MRI sequences successfully capture most acute structural abnormalities, a number of subacute spinal pathologies may be much more difficult to detect. Spinal cord infarction can be challenging to confirm in the acute phase and repeated spinal imaging is often performed to ascertain the diagnosis. Subtle changes following whiplash injury are not always readily visualized despite clinical evidence of myelopathy [8].

In sharp contrast with the above acute conditions, spinal imaging has relatively limited value in confirming progressive neurodegenerative cord pathologies, such as spinal muscular atrophy, primary lateral sclerosis (PLS), hereditary spastic paraplegia, dorsal root ganglionopathy, HTLV-1 associated myelopathy, amyotrophic lateral sclerosis (ALS), spinocerebellar ataxia or HIV vacuolar myelopathy.

The meaningful interpretation of cord atrophy is notoriously difficult and remains largely subjective in the absence of quantitative metrics. Qualitative cues may be nonspecific and require careful appraisal. The specificity and sensitivity of 'owl's eyes' or 'snake's eye' signs on axial imaging is relatively poor but may indicate cord infarction, PLS or ALS in the appropriate clinical context [9]. Similarly, the 'inverted V sign' or hyperintensities of the dorsal columns is nonspecific and may be observed in subacute combined degeneration of the cord, copper deficiency myeloneuropathy and tabes dorsalis. Inferior cervical cord atrophy, anterior shifting of the posterior wall of the dural canal and enlarged posterior epidural compartment observed in flexion MR studies may indicate Hirayama disease, but similar findings may also be observed following trauma [10,11].

Future directions and novel imaging methods

Patients presenting with slowly progressive spastic paraparesis or severe sensory ataxias often have limited findings on routine spinal imaging despite clinical evidence of a progressive myelopathy. Patients presenting with HIV myelopathies often present with significant clinical disability despite fairly nonspecific MRI findings. Patients with hereditary spastic paraparesis, HTLV infection, West Nile poliomyelitis all suffer from considerable myelopathies, yet may only exhibit nonspecific MR alterations on standard imaging [12]. ALS patients with tragically progressive spinal pathology only show subtle cord atrophy on routine spinal imaging [13,14]. PLS patients with considerable gait impairment may exhibit hyperintensities in the lateral corticospinal tracts but

their gait impairment is often out of proportion to their imaging findings. Similarly, the diagnosis of dorsal root ganglionopathy may remain elusive despite progressive and selective cord atrophy [15]. In summary, a relatively large group of sinister and progressive spinal conditions exist where standard spinal MRI has remarkably little to offer. This is in striking contrast with the detection rates of advanced quantitative techniques used in a research setting.

In ALS, spinal MRS detects presymptomatic metabolic changes in mutation carriers [16], measures of cord atrophy correlate with clinical disability [17], diffusion tensor imaging (DTI) captures longitudinal changes [18], MRS correlates with clinical disability [19], and combined diffusion tensor and cross-sectional area measures have been repeatedly proposed as sensitive biomarkers of disease progression [20]. In traumatic neck injuries, DTI, high angular resolution diffusion-weighted imaging and magnetization transfer imaging show promise in capturing pathology [21]. While DTI primarily evaluates the longitudinal fibers of the cord, q-ball imaging promises to characterize the commissural and dorso-ventral fibers in the spinal cord [22]. In multiple sclerosis, magnetization transfer imaging [23], DTI fiber tractography [24], myelin water fraction estimation [25] and DTI metrics [26] have all been successfully correlated with clinical metrics. Spinal functional MRI has been applied both to multiple sclerosis [27] and chronic incomplete spinal cord injury [28]. The majority of quantitative spinal cord MRI studies are undertaken in ALS, MS and spinal cord injuries and very few dedicated imaging studies can be identified in hereditary spastic paraparesis and spinocerebellar ataxias [29].

Conclusions

The relentless methodological advances from pneumomyelography to cord tractography indicate that we are likely to witness continued progress in the field. Despite recent developments, an urgent and unmet need persists for sensitive spinal measures. These markers are indispensable for accurate clinical monitoring, pharmaceutical trial end points, and for the development of viable diagnostic and prognostic indicators.

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