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Commentary Open Access

Proton Nuclear Magnetic Resonance (NMR) Metabolomics: Future in Etiological Diagnosis of Encephalomyelitis

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Introduction

Encephalomyelitis is relatively rare (10.5-13.8/100,000 children) but may be fatal, and frequently causes permanent disability. The cause remains unknown in more than half the cases [1,2].

Cardinal symptoms of encephalitis include fever, headache, neck stiffness, photophobia, confusion and seizures. Clinical examination will reveal altered mental status ranging from somnolence to lethargy and coma. Delirium, cranial nerve palsies, ataxia, rash and sign of increased intracranial pressure may be seen. It is not always possible to ascertain the specific cause of encephalitis from clinical presentation alone. However there are features that can give some clue to possible etiology. Arbovirus encephalitis often heralds with a flu-like syndrome followed by increasing confusion and stupor. Herpes simplex encephalitis often presents with an abrupt change in behavior, memory loss, focal or generalized seizures, and speech concerns. West Nile encephalitis may present with flaccid, asymmetric motor weakness with altered sensorium of variable degree. Varicella may manifest with cerebellar features as Japanese encephalitis presenting with basal ganglia symptoms

The current evaluation of encephalomyelitis requires a battery of tests including neuroimaging, expensive and often limited by the inability to obtain enough specimens in pediatric population along with unacceptable turnaround time. It is warranted to explore newer methodologies to establish early diagnosis, which is detrimental to favorable clinical outcome.

Proton NMR Metabolomics

The concept that biological fluids reflect the health of an individual has existed for a long time. Nuclear Magnetic Resonance (NMR) spectroscopy is based on measuring the absorption of light (radio waves) due to changes in nuclear spin orientation of molecules of different metabolites. Proton nuclear magnetic resonance (NMR) metabolomics can be used to study metabolic profile of cerebrospinal fluid and urine. NMR is fully quantitative, highly reproducible, and detects all metabolites simultaneously in one snapshot. The samples are completely recoverable. Distinct Cerebro Spinal Fluid (CSF) metabolomics profile for normal controls, human rabies,[6] West Nile encephalitis, and Lyme meningitis have been well described.

One can correlate CSF and urine metabolomics with clinical course, imaging, and laboratory findings, to develop a rapid screen to differentiate infectious from auto-inflammatory and autoimmune causes of encephalomyelitis by cluster analysis.

We have already used proton nuclear magnetic resonance (H^+-NMR) to identify and quantify 56 metabolites from normal and diseased CSF using 0.5 ml of CSF in under 2 hours, and discriminate a CSF metabolomics profile by unsupervised (unbiased) cluster analysis.

Contrast this with the standard diagnostic approach –almost a century old-- of quantifying two (2) substances (glucose and protein) from the same CSF volume with similar turn-around time.

Preliminarily, we can with high accuracy discriminate 6 central nervous system (CNS) diseases using NMR metabolomics. Contrast this with turn-around time of 4-7+ days for conventional encephalitis testing for oligoclonal bands, serology for EBV, Varicella Zoster Virus (VZV) or Lyme disease, and N-methyl-D-aspartate receptor (NMDAR), Voltage –gated potassium channel (VGKC) or aquaporin-4 autoantibodies.

We conducted a study of CSF metabolomics comparing persons under treatment for rabies encephalitis, to normal controls. We were able to describe a metabolomic profile for human rabies across a number of weeks of illness. We also identified metabolic changes that correlated with clinical worsening or, alternatively, with survival. More recently, we compared CSF metabolomics profiles from patients without infection, rabies encephalitis, West Nile encephalitis, Lyme meningitis, fungal meningitis, malaria encephalopathy, and multiple sclerosis

CSF profiles clustered well and were surprisingly distinct between diseases. We hypothesize that these same findings may hold true for other forms of infectious encephalitis and will cleanly distinguish these from (ADEM) acute disseminated encephalomyelitis (approximating MS)

We do not intend to supplant highly accurate and definitive testing for specific viruses or autoantibodies, but NMR might accelerate and focus initiation of effective therapies, to improve outcomes, and improve patient safety and financial risk by limiting expensive, CSF- or blood-consuming diagnostics.

Discussion

The common infectious cause of encephalitis, like herpes simplex virus (HSV), requires specific antimicrobial therapy. However, vast numbers of infectious agents do not have specific treatment, and damage is inflicted by autoimmune mechanism, which requires immunosuppression and supportive therapy. Recent epidemiological revision suggests that the most common form of encephalitis is caused by an autoantibody directed at the NMDA class of glutamate receptors (NMDAR) in the brain [3]. Autoimmune encephalitis can follow HSV encephalitis [4] which can make clinical decisions more difficult.

Acute disseminated encephalomyelitis (ADEM), which often follows mild systemic illnesses, vaccination, or trauma, is a form of encephalomyelitis characterized by multifocal white matter damage af-

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fecting the myelin. The inflammation is mediated by cellular immunity [5], and treatment varies considerably from antibody-mediated disease. Lyme disease may mimic ADEM with multifocal appearance, requiring antibacterial therapy rather than immunosuppression. Encephalopathy mimics encephalomyelitis, but is caused by entirely different etiologies, like metabolic and endocrine disorders to name few.

Given the lack of early distinct clinical findings in the above situations, coupled with expensive array of tests with need to send multiple samples to different reference labs and slow turnaround time, selecting appropriate therapy in timely manner is challenging. It's a frequent clinical dilemma, whether to treat encephalitis as an infection, or initiate immunosuppression, which are contradictory [6].

What is needed is broadly targeted screening tests that can be readily available in most countries at a local level. NMR metabolomics has potential to evolve into useful tool in these conditions. Specific confirmatory tests can follow. Pathogen-discovery methods by next generation sequencing [7,8] show tremendous promise but require expensive instrumentation and computer resources, generate massive data, and require major informatics support.

Mass spectroscopy is more accessible locally, but requires derivitization of samples. CSF is contaminated with a cephalocaudal gradient of serum proteins that challenges interpretation. NMR metabolomics is a complementary strategy that requires minimal processing, sample volume and time. NMR instruments are widely distributed in many emerging countries and the spectra are compact data that are easily transmitted by Internet. Analysis can be done on laptops using conventional statistical software.

References

1. Venkatesan A, Tunkel AR, Bloch KC, Lauring AS, Sejvar J, et al. (2013) Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. Clin Infect Dis 57: 1114-1128.
2. Kneen R, Michael BD, Menson E, Mehta B, Easton A, et al. (2012) Management of suspected viral encephalitis in children - Association of British Neurologists and British Paediatric Allergy, Immunology and Infection Group national guidelines. J Infect 64: 449-477.
3. Suleiman J, Brilot F, Lang B, Vincent A, Dale RC (2013) Autoimmune epilepsy in children: case series and proposed guidelines for identification. Epilepsia 54: 1036-1045.
4. Pruss H, Finke C, Holtje M, Hofmann J, Klingbeil C, et al. (2012) N-methyl-D-aspartate receptor antibodies in herpes simplex encephalitis. Ann Neurol 72: 902-911.
5. Pohl D, Tenembaum S (2012) Treatment of acute disseminated encephalomyelitis. Curr Treat Options Neurol 14: 264-275.
6. O'Sullivan A, Willoughby RE, Mishchuk D, Alcarraz B, Cabezas-Sanchez C, et al. (2013) Metabolomics of cerebrospinal fluid from humans treated for rabies. J Proteome Res 12: 481-490.
7. Brown JR, Morfopoulou S, Hubb J, Emmett WA, Ip W, et al. (2015) Astrovirus VA1/HMO-C: an increasingly recognized neurotropic pathogen in immunocompromised patients. Clin Infect Dis 60: 881-888.
8. Wilson MR, Naccache SN, Samayoa E, Biagtan M, Bashir H, et al. (2014) Actionable diagnosis of neuroleptospirosis by next-generation sequencing. N Engl J Med 370: 2408-2417.

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