Similarity Network Fusion

A Novel Application to Making Clinical Diagnoses

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KEYWORDS

• Similarity network fusion • Analysis • Classification • Immune-mediated disease

KEY POINTS

- Similarity Network Fusion (SNF) is a useful analytical tool to group patients together and understand patient characteristics.
- SNF uses different data types and is therefore helpful in classifying patients when diagnoses may be difficult to determine or understand.
- SNF represents a novel computational analytical method that may assist with understanding similarities and differences between patients and extends beyond classification criteria and working diagnoses.

INTRODUCTION

Systemic autoimmune processes are challenging conditions to diagnosis accurately, monitor, and treat. Many of these conditions present within the pediatric age range and can contribute to significant morbidity if not diagnosed promptly and managed appropriately. Systemic lupus erythematosus (SLE) represents one such condition that affects 3.3 to 8.8 cases per 100,000 children.[1] It is a noncurative disease with many systemic features that are burdensome to the child and those involved in his or her care. It is diagnosed using a set of clinical and serologic classification features

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that were officially developed in 1971 but continue to evolve and to be revised.[2,3] The waxing and waning pattern of this chronic disease poses a challenge to those involved with monitoring its course, since the disease also progresses and symptoms evolve over time.

Similarly, many autoimmune conditions are diagnosed based on an established constellation of clinical and serologic features. The broad spectrum of presenting symptoms within which to identify diagnostic features can pose a challenge in knowing how to best manage and classify patient diseases. For example, autoimmune hepatitis (AIH) can present with a combination of fatigue, abdominal pain, weight loss, anorexia, fever, and jaundice.[4] These symptoms are also found in patients with rheumatologic disorders such as systemic lupus erythematosus (SLE). In this instance, the nonspecific features make a clinical diagnosis difficult to achieve.

Immune-mediated diseases can also progress to involve additional organs that would not classically be attributed to the working diagnosis. Because autoimmune conditions tend to predispose patients to developing other autoimmune conditions, clinicians may find themselves wondering whether new organ involvement represents a severe form of the primary disease or the first presentation of an additional autoimmune disorder. A better understanding of what the evolving process of such conditions should be and what should be considered a separate disease entity is necessary. This would enable more accurate prognostication and explanation to patients and families around the management of their chronic disease. As an example, the etiology of liver involvement in patients with SLE represents one of these unanswered challenges.

Initially coined lupoid hepatitis, autoimmune hepatitis (AIH) represents one such condition.[5] Numerous conflicting studies have tried to describe the extent of liver disease that could be attributed to SLE before its features would be better defined as a primary liver disease. The conclusion from Runyon and colleagues[6] is that liver disease can be significant in SLE and that a separate entity termed lupoid hepatitis should not be considered. Gibson and colleagues[7] had the opposite feeling and concluded that liver disease was mainly subclinical in SLE and that anything more pronounced would correspond to a separate disease entity. A prospective study by Miller and colleagues[8] supported both MacKay's initial paper and the conclusion drawn by Gibson and colleagues, finding that only mild liver disease could be attributed to the spectrum of SLE. The medical advances of the next 2 decades only contributed additional confusion to the description of what should be considered lupoid hepatitis and what should be labeled SLE-associated hepatitis (or lupus hepatitis). Little distinguishes the 2 clinical presentations to this day.

The difficulty in defining these 2 diseases as distinct entities is that there are more unifying than dividing features. The clinical presentations, the liver biopsy findings and the autoantibody profile appear to be interchangeable between diseases.[9–16] The same conflicting findings have been evident within the pediatric literature.[14,17–19] Another challenge may be attributed to the fact that these diseases are diagnosed according to classifications of features determined by consensus expert opinion.[3,20–22]

There is the potential for an inherent flaw in defining these diseases based on expert opinion-driven clinical criteria. Clinically, patients with autoimmune diseases that manifest with multiorgan involvement may receive a diagnosis based on the specialist to whom they are initially referred. The patient who presents with elevated liver enzymes and systemic features may be referred to a hepatologist and be given a diagnosis of autoimmune hepatitis (AIH). The same patient could be given the diagnosis of SLE with liver involvement if first referred to a rheumatologist. Both clinicians are challenged with the task of applying complex predefined classification to best explain the

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