Juvenile idiopathic arthritis: a heterogenous group of diseases with a heterogenous set of challenges

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Arthritis affects children too. As a matter of fact, juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease, or disease affecting joints and connective tissue, found in children with a prevalence of 16-150 per 100,000 individuals in developed countries [1]. Encompassing all forms of arthritis with unknown etiology that are found in patients aged 16 years and younger, and that persists for more than 6 weeks at a time, JIA is used as an umbrella term to describe a heterogenous group of diseases that are categorized according to a wide range of laboratory and clinical diagnostic criteria, including the number of joints involved, fever, and lymph node enlargement [2]. Currently, there are seven subtypessystemic arthritis (sJIA), enthesitis related arthritis (ERA), oligoarthritis, rheumatoid factor-positive (RF+) polyarthritis, rheumatoid factor-negative (RF-) polyarthritis, psoriatic arthritis, and undifferentiated arthritis [2].

Despite marked advances in management and treatment, JIA remains a disease that results in functional impairments (reduced range of motion, joint swelling, growth abnormalities, etc.), medication-associated morbidity, and long-term disabilities that can incur lasting economical and emotional strain on patients and their families [3]. On average, the annual cost of treating JIA ranges between approximately $3000 to $18 000 per year and can climb even higher for patients receiving biologic agents, such as monoclonal antibodies [4]. In addition to financial costs, JIA takes a toll on quality of life. The lives of children with chronic arthritis are impacted by ambulatory visits, hospitalizations, and interruptions in education, which in turn, augments the burden on their caregivers.

The high degree of inter-patient heterogeneity in clinical manifestations, gene expression, and cellular phenotypes brings about numerous hurdles in differential disease diagnosis and treatment. To begin, recognition of JIA in children can be challenging in itself and it often takes a long time for children who develop this disease to obtain a referral for a pediatric rheumatologist, and a subsequent assessment. Owing to its definition, diagnosis of JIA does not occur prior to 6 weeks of symptom onset, and often is not completed until much later. In British Columbia, Canada, the median amount of time between symptom onset and obtaining a pediatric rheumatologist assessment is 38.3 weeks—almost 9 months [5].

As the most recent system of JIA classification, the diagnostic criteria put forward by the International League of Associations for Rheumatology (ILAR) are based upon clinical manifestations (as mentioned above) [2]. It has been proposed that additional measures are needed to pinpoint the exact condition a child may have in this broad group of diseases [6]. For example, systemic JIA (sJIA) is distinct in the systemic features and inflammatory response that it displays, so much so that there is an up-and-coming consensus for it to be set apart from the other subtypes [7]. The heavy involvement of the innate immune system, along with the major roles that interleukin (IL)-6, IL-1, and IL-18 play, has led many to believe that sJIA should be considered as an autoinflammatory syndrome rather than a classic autoimmune disease like systemic lupus erythematosus (SLE) [7]. Furthermore, due to such findings, and to the knowledge that has been acquired since the introduction of the ILAR classification system, some believe that it is only a matter of time before the all-encompassing term "juvenile idiopathic arthritis" will be phased out [8].

In addition to healthcare practitioners, parents of children who develop JIA also face barriers in understanding JIA pathogenesis. In a study where parental education was used as a measure of socioeconomic status, it was found that the children of parents who had either a university degree or post-graduate training were more likely to be seen by a rheumatologist sooner than those of parents with less education, and is perhaps attributable to their increased mindfulness of clinical abnormalities or familiarity with the healthcare system [9]. This highlights the benefits of educational efforts in promoting awareness of presenting symptoms of JIA that could help parents recognize when to seek medical attention.

The heterogeneity of conditions found within JIA and the classification of diseases creates large compilations of data that pose analytical challenges. Machine learning

methods that take both clinical and biological factors into consideration, have been tested in the development of novel approaches that could be used to dissect these large data sets [10]. High-throughput data analysis could radically improve the efficacy and accuracy of future diagnoses made in the clinic. Such advances could also warrant the development of personalized therapy for patients with JIA, minimizing the time spent arriving at an accurate diagnosis and determining the best courses of therapy. More importantly, children with JIA would not have to wait as long to receive the appropriate treatment, thereby reducing the amount of joint damage that they experience when living with arthritis. Further investigation into the underlying genetic and cellular mechanisms that drive specific JIA phenotypes is needed in order to determine more effective methods for tackling this life-impacting group of diseases.

From a whole-diet perspective, dietary patterns that are high in plant-based foods and lean proteins, and that are based on consuming fresh and minimally processed foods, such as the Mediterranean diet, have garnered attention in the field of nutritional psychiatry for improving mental health. Jacka and colleagues recently conducted a randomized controlled trial (SMILES trial) and showed that a modified Mediterranean diet support group had a greater improvement in the symptoms of depression in clinically depressed individuals than a social support group [8]. Parletta and colleagues also conducted a trial (HELIFMED) comparing a Mediterranean-style dietary intervention and a social support condition as a control, and found similar results [9]. Unsurprisingly, the Mediterranean diet is rich in nutrients that are potentially linked to improved mental health, and that have been consistently associated with lower levels of inflammation.

Although the research to date that directly implicates nutrient intake and diet with improved symptoms of depression is by no means conclusive, it may eventually present an enticing alternative treatment option for MDD. Improving nutrient intake by modifying diet is an accessible lifestyle change with no adverse side effects and may translate to improved mental health. These lifestyle changes have considerable implications for individuals who are unable or do not wish to take antidepressant medication. Moreover, individuals who maintain a healthy diet are more likely to engage in other protective health behaviours that may also help to improve mental health. For these reasons, research on the impact of diet on MDD should focus on clinical populations, and should be considered in clinical settings for the treatment of mental illness.

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