Multimodal Analysis Revealed Altered Brain Connectivity Patterns and Neuroinflammatory Processes in the Background of Difficult-To-Treat Rheumatoid Arthritis

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BACKGROUND AND AIMS

Despite recent advancements in therapy of rheumatoid arthritis (RA), approximately 5–30% of patients with RA remain symptomatic and are classified as difficult-to-treat (D2T).[1] Difficult-to-treat RA (D2T RA) is a complex and heterogeneous disease state with several possible contributing factors, including immunological heterogeneity, maladaptive central pain processing, the presence of comorbidities, psychological disturbances, or socioeconomic factors. However, the exact mechanisms driving this disease phenotype remain poorly understood. The authors' study aimed to investigate the underlying factors behind the D2T condition, potentially revealing the connections between pain and inflammation with a multimodal approach.[2]

MATERIALS AND METHODS

A total of 31 patients with D2T RA (defined by the 2020 European Alliance of Associations for Rheumatology [EULAR] criteria), 18 patients with non-D2T RA, and 32 healthy controls were included. All participants underwent detailed clinical assessment, psychological evaluation (including in-depth interviews, standardized questionnaires, and the Rorschach test), resting-state functional MRI (fMRI) scans before and after standardized heat pain stimulation, as well as peripheral blood transcriptomic and plasma metabolomic analyses.

RESULTS

Resting-state functional MRI demonstrated significantly reduced intrinsic connectivity of the posterior cingulate cortex in RA, most pronounced in the D2T subgroup. Following acute painful stimulation, posterior cingulate cortex connectivity increased in D2T RA but decreased in non-D2T RA and healthy controls, overall suggesting alterations in the baseline and pain-related connectivity of the default-mode network in D2T RA. Seed-based analysis of the postcentral gyrus revealed a reduction in connectivity strength across many connections within the somatosensory area, which were significantly altered after pain stimulation in all patients with RA compared to healthy controls. Fractional amplitude of low-frequency fluctuations analysis further identified reduced activity in several brain regions (e.g., lateral occipital cortex, middle frontal gyrus, medial prefrontal cortex, and frontal pole) among patients with RA, with the most significant decreases in D2T RA. Compared to non-D2T RA, D2T patients also exhibited lower fractional amplitude of low-frequency fluctuations in additional brain regions, indicating more complex alterations in pain and somatosensory processing, behavior, and cognitive functions. The authors' psychological results also strengthened these findings by demonstrating that D2T patients are characterized by maladaptive coping strategies, reduced motivation, negative outlook, and altered cognitive control. Peripheral transcriptomic profiling identified 87 differentially expressed mRNAs (70 downregulated, 17 upregulated) in D2T RA versus non-D2T RA comparisons, many of which could be linked to processes related to neuroinflammation, synaptic plasticity, or neuronal development (e.g., NRG1, S100B, or CDK5), which was also demonstrated by functional enrichment analysis. Metabolomic profiling revealed altered amino acid and sphingolipid metabolism, further supporting the roles of inflammatory and neuronal signaling pathways in the development of D2T RA.

CONCLUSION

Overall, this integrative, multimodal approach identified mechanisms related to the central nervous system that potentially contribute to the development of D2T RA. This disease state can be characterized by altered brain connectivity patterns, characteristic psychological features, and distinct

transcriptomic and metabolomic profiles, which could provide a basis for improving patient stratification, identifying new biomarkers, and developing novel therapeutic strategies targeting central mechanisms. Furthermore, understanding and addressing these central contributors may improve outcomes for patients who are D2T.

References

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