Universiteit
Leiden
The Netherlands

Cervical spine deformity in patients with rheumatoid arthritis: from prevention to prediction

Lebouille-Veldman, A.B.

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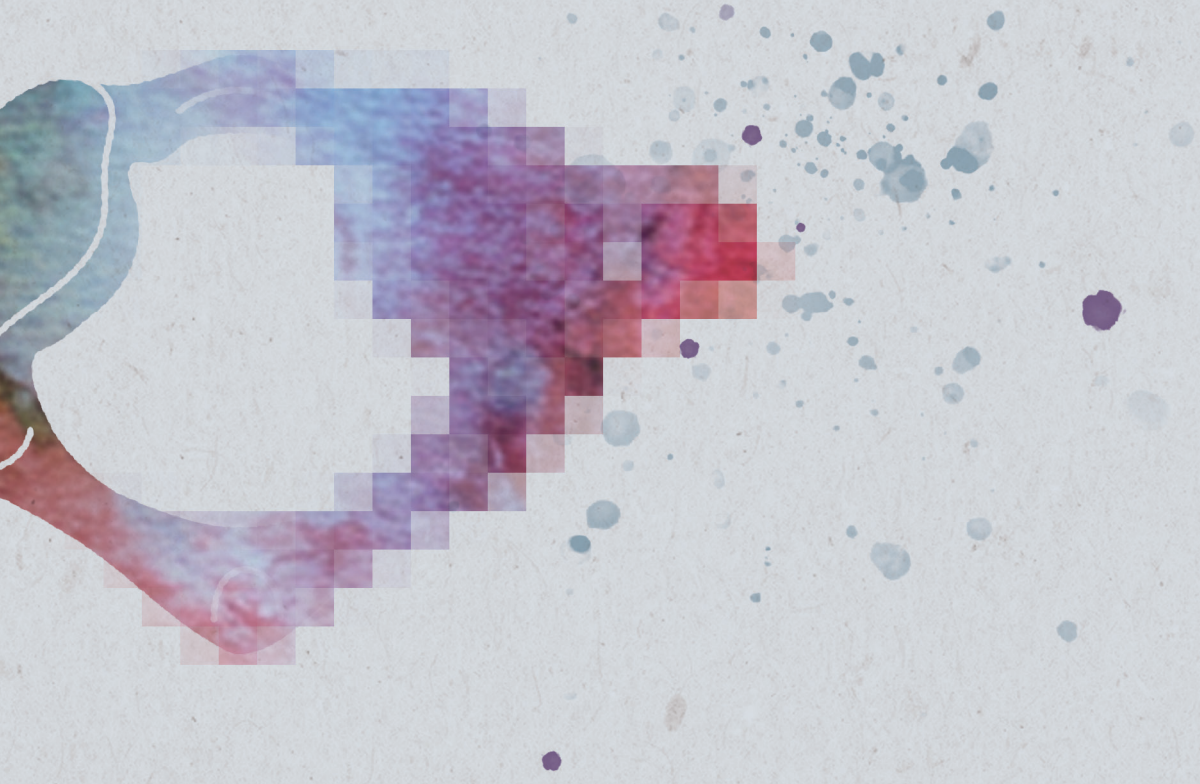

APPENDICES

Summary

Rheumatoid arthritis (RA) is a chronic inflammatory disease that causes progressive articular damage. The cervical spine consists of vertebrae, stabilized by intervertebral discs, joints and an intricate network of ligaments. In patients with RA, these ligaments can become inflamed. This can lead to the development of RA associated cervical spine deformity, which is defined by the presence of atlantoaxial subluxation (AAS), subaxial subluxation (SAS) and/or vertical translocation (VT). In AAS, there is subluxation between the C1 and C2 vertebrae. If vertical subluxation of the C2 vertebra develops, VT is present. In SAS, subluxation of vertebrae in the subaxial spine (C2-C7) is present. RA associated cervical spine deformity can lead to pain in the back of the head (occipital neuralgia), weakness of the limbs, tingling and in some cases paralysis.

This thesis aimed to research and describe the possible relationship between cervical spine deformity in RA and systemic disease activity. Also, potential influence of different medications on cervical spine deformity was studied. Risk factors for cervical spine deformity in RA were researched using classical statistics, as well as using a deep learning model to work towards prediction of cervical spine deformity.

A systematic evaluation of literature did not provide us with a satisfactory answer to the question whether control of systemic disease activity in rheumatoid arthritis also prevents RA-associated cervical spine deformity, besides damage to other joints. Another observation from literature is that data suggest that lowering DAS values did not halt progression once cervical spine deformity was present.

In current practice, it appears that the number of surgeries to correct RA associated cervical spine deformity is declining. It has been hypothesized that deformities like AAS, SAS and VT rarely exist in the Western world with the introduction of new treatment methods for patients with RA, such as biological DMARDs. However, this thesis shows that these deformities, although less prevalent, do still exist and it is currently unknown which patients with RA are at risk of developing cervical spine deformity. Analysis of the BeSt Trial—a Dutch RCT that treated patients with early RA intensively targeting low DAS values—revealed a surprisingly high prevalence (40% for AAS and/or SAS > 2mm) of cervical spine deformity, including severe cases (3%), despite strict treat to target strategy. Moreover, the relationship between DAS and cervical deformity was not straightforward: neither mean DAS nor disease flares

reliably predicted deformity, although patients with more flares surprisingly showed a trend toward lower odds of deformity. This counterintuitive result may be due to treatment intensification following flares, especially with biologicals such as infliximab. This challenges the hypothesis that treat-to-target strategy using only DAS might not be the safest option to protect the cervical spine in RA.

Subsequent analyses using the data from the BeSt Trial found that prolonged use of infliximab was significantly associated with reduced odds of cervical spine deformity. Specifically, each additional year of infliximab use reduced the odds of deformity being present after 10 years by 11%. In contrast, long-term glucocorticoid use was associated with increased risk of cervical deformity. These findings align with evolving treatment guidelines, such as the ACR's recommendation to limit glucocorticoid use due to systemic toxicity.

Since it has been shown in this thesis that RA-associated cervical spine deformity still exists, even in this time of biological DMARDs, it is important that patients with cervical spine deformity can be identified easily and quickly. This thesis therefore explored the possibility to use artificial intelligence (AI) to screen imaging of RA patients in a more standardized matter. An experimental study was performed to develop a novel automated segmentation model of the cervical spine of RA patients. The performance reached with this model was moderate, since the anatomical complexity of the C1 and C2 vertebrae and its limited X-ray visibility decreased possible clinical utility of the model.

A more promising direction involved a deep learning model trained on MRI scans of RA patients before or at the start of the disease, to predict the development of cervical spine deformity. This model achieved high accuracy (0.84) and good sensitivity/specificity, suggesting feasibility for early risk stratification—though external validation is still required.

Future research directions include standardizing definitions of cervical deformity and studying the coherence between clinical and radiological indicators of cervical spine deformity. Broader goals include developing robust, externally validated, user-friendly AI tools for screening and prediction of cervical spine deformity in RA patients, and reconsidering treatment strategies and goals to better safeguard the cervical spine.