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PERSPECTIVE

# A Nordic screening guideline for juvenile idiopathic arthritis-related uveitis

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**Abstract**

**Purpose:** The purpose of this perspective was to shed light on screening of uveitis among Nordic children with juvenile idiopathic arthritis (JIA).

**Methods:** A literature search was conducted to review predictors of JIA-uveitis and previous JIA-uveitis screening recommendations.

**Results:** Predictors of uveitis in JIA are younger age and positive antinuclear antibody titre at onset of JIA, specific subtypes of JIA (extended and persistent oligoarthritis, rheumatoid factor negative polyarthritis and psoriatic arthritis) and short duration of JIA. Methotrexate and monoclonal tumour necrosis factor (TNF) inhibitor treatment reduce the risk JIA-uveitis.

**Conclusion:** Children with all of the above risk factors should be screened frequently but if they receive TNF inhibitor or methotrexate therapy, they may be screened less frequently. Children with none of the risk factors do not benefit from long-term screening for uveitis. A guideline for intervals and overall length of screening was prepared considering currently known risk factors for JIA-uveitis, the Nordic population and previous guidelines.

**KEYWORDS**
juvenile idiopathic arthritis, methotrexate, screening, TNF inhibitors, uveitis

Uveitis is a common manifestation of juvenile idiopathic arthritis (JIA) in Nordic countries, Central Europe and United States (10–22%; Angeles-Han et al., 2015; Rypdal et al., 2020; Tappeiner et al., 2016). In addition to a Nordic origin, other predictors of uveitis in JIA are young age and positive antinuclear antibody (ANA) titre at onset of JIA, specific subtypes of JIA (Table 1) and short duration of JIA (Angeles-Han et al., 2015; Heiligenhaus et al., 2007; Nordal et al., 2017; Tappeiner et al., 2018). Treatment with methotrexate, monoclonal tumour necrosis factor (TNF) inhibitors or both significantly reduces the risk of JIA-uveitis (Kostik et al., 2016; Papadopoulou et al., 2013; Tappeiner et al., 2016, 2018).

Anterior uveitis associated with JIA is a potentially sight-threating disease. Ocular complications that result from chronic uveal inflammation and its treatment are common in JIA-uveitis. JIA-related uveitis is a predominantly asymptomatic disease before vision loss occurs. Therefore, children with JIA are routinely screened for uveitis (Angeles-Han et al., 2015; Edelsten et al., 2002; Heiligenhaus et al., 2007; Kanski, 1988). Prognosis of JIA-uveitis has been improved with early screening, with monoclonal TNF-inhibitor treatment and with improved surgical techniques (Edelsten et al., 2002; Sherry et al., 1991, Heiligenhaus et al., 2012; Tappeiner et al., 2016; Wennink et al., 2022).

Previous screening guidelines for uveitis in JIA have included the following risk factors: subtype of JIA, age and ANA titre at onset of JIA, and duration of JIA. Systemic-onset arthritis and RF-positive arthritis have been included in screening guidelines, although uveitis is a very rare or non-existent manifestation of them. Enthesitis-related arthritis (ERA) has been considered a low to moderate-risk disease because two-thirds of patients with ERA-related uveitis are symptomatic. Therefore, although up to 25% of Nordic patients with ERA may develop uveitis, ERA has been grouped with systemic-onset arthritis and RF-positive arthritis in uveitis screening (Angeles-Han et al., 2015; Heiligenhaus et al., 2007; Leinonen, 2020; Nordal et al., 2017).

Uveitis occurs most commonly (82–90%) during the first 4 years after the onset of arthritis (Heiligenhaus et al., 2007; Kotaniemi et al., 2001; Nordal et al., 2017; Rypdal et al., 2020). Therefore, screening guidelines

**TABLE 1** Rates of different subtypes of juvenile idiopathic arthritis and rates of uveitis in each subtype, following the International League of Associations for Rheumatology Criteria (Angeles-Han et al., 2015; Glerup et al., 2022; Heiligenhaus et al., 2007; Petty et al., 2004; Rypdal et al., 2020; Tappeiner et al., 2016).

| Subtype of JIA | Rate of the subtype | Rate of uveitis | Risk of uveitis |
|---|---|---|---|
| Persistent oligoarthritis | 46–54% | 41–46% | High |
| Extended oligoarthritis | | | |
| RF-negative polyarthritis | 12–18% | 5–23% | |
| Psoriatic arthritis | 4–8% | 10–36% | |
| Enthesitis-related arthritis | 10–12% | 7–25% | Moderate |
| Systemic-onset arthritis | 4–8% | 0% | Very low |
| RF-positive polyarthritis | 1–5% | 0–2% | |
| Undifferentiated arthritis | 1–7% | 0–20% | Unknown |
| All | | 10–22% | |

Abbreviations: JIA, juvenile idiopathic arthritis; RF, rheumatoid factor.

recommend more frequent screening during the first 2–4 years and less frequently thereafter (Angeles-Han et al., 2019; Heiligenhaus et al., 2007; Leinonen, 2020). No study has examined different JIA-uveitis screening intervals. Screening intervals are set at 3, 6 and 12 months because they are clinically convenient intervals and reflect a multiplied risk of uveitis among high-risk patients. High-risk patients are screened every 3 months, moderate-risk patients every 6 months and low-risk patients every 12 months (Angeles-Han et al., 2019, Heiligenhaus et al., 2007, Leinonen, 2020).

Screening is generally continued for 7 years or until the child reaches 16 years of age (Heiligenhaus et al., 2007; Leinonen, 2020). The American College of Rheumatology guideline does not give guidance on the total length of the follow-up (Angeles-Han et al., 2019). A more detailed guideline for the length of screening seems necessary considering how the age at onset of JIA impacts the risk of uveitis. Children who are >6 years of age at onset of JIA have a lower risk of uveitis to start with but also, they do not appear to develop uveitis after 2 years of follow-up (Heiligenhaus et al., 2007). Thus, 2 years of screening should be sufficient for children who are >6 years of age at onset of JIA. For children who have a high risk of uveitis because of type of JIA, young age and positive ANA titre at onset, 16 years may be a more appropriate age to discontinue screening and start self-monitoring. The Nordic Study Group of Paediatric Rheumatology suggested that systematic screening for JIA-uveitis should be extended. In the Nordic JIA cohort, 12 of 434 patients had a late-onset uveitis at a mean age of 23 years, 8–18 years after the onset of JIA (Rypdal et al., 2020). Considering the additional 10 years of follow-up and that ≥5 of these 12 patients had ocular symptoms, it is not reasonable to provide systematic JIA-uveitis screening for asymptomatic adults. Adults with JIA should be informed that if any ocular symptoms occur, they should be screened for uveitis.

Disease-modifying antirheumatic drug (DMARD) therapy has not been factored in as a risk factor in previous screening guidelines (Angeles-Han et al., 2019; Heiligenhaus et al., 2007; Leinonen, 2020). Methotrexate treatment associates with a reduced risk (HR 0.14–0.63) of JIA-uveitis (Kostik et al., 2016; Papadopoulou et al., 2013; Tappeiner et al., 2016, 2018). Monoclonal TNF-inhibitor treatment with adalimumab reduces the risk of uveitis in JIA as a monotherapy and as a combination with methotrexate (HR 0.09) compared with no DMARD treatment in the year before the onset of uveitis (Tappeiner et al., 2018). Etanercept, a TNF inhibitor which is not a monoclonal antibody, does not alter the risk of uveitis (Klotsche et al., 2016; Tappeiner et al., 2016, 2018).

A more detailed screening guideline was developed to reduce unnecessary screening for moderate to low-risk children who are treated with methotrexate or monoclonal TNF inhibitors and children who have systemic-onset arthritis, RF-positive polyarthritis or who are >6 years old at onset of arthritis.

The following recommendations can be made based on the current literature:

1. Children with recently diagnosed JIA or suspicion of JIA should be screened without delay (Edelsten et al., 2002).
2. Risk factors should determine the screening interval. Risk of asymptomatic uveitis is highest among children (Angeles-Han et al., 2015; Heiligenhaus et al., 2007; Nordal et al., 2017; Tappeiner et al., 2016, 2018)
   a. with persistent or extended oligoarthritis, RF-negative polyarthritis, psoriatic arthritis, or undifferentiated arthritis and
   b. who were ≤6 years of age at onset of JIA and
   c. who had a positive ANA titre at diagnosis of JIA and
   d. whose duration of JIA has been ≤4 years prior the screening visit and
   e. who are **not** receiving methotrexate or monoclonal TNF-inhibitor treatment.
3. Children with all five risk factors (a-e) have a very high risk of uveitis and they should be screened every 3 months for 2–4 years after onset of JIA (Angeles-Han et al., 2015, 2019; Heiligenhaus et al., 2007; Kotaniemi et al., 2001; Nordal et al., 2017).
4. Children with risk factors a, b and e or a, c and e have the second and third highest risk for JIA-uveitis and may be screened every 6 months for 2–4 years after onset of JIA (Angeles-Han et al., 2015; Heiligenhaus et al., 2007; Nordal et al., 2017; Rypdal et al., 2020).
5. Children with risk factor a only, and children with enthesitis-related arthritis have a low risk of asymptomatic uveitis and they may be screened every 12 months (Angeles-Han et al., 2015; Heiligenhaus et al., 2007; Nordal et al., 2017).
6. Children with systemic-onset or RF-positive arthritis do not need additional screening if they do not have uveitis at first screening (Angeles-Han et al., 2015, Heiligenhaus et al., 2007, Nordal et al., 2017).
7. Children >6 years of age at onset of JIA (without risk factor b) are not likely to develop uveitis >2 years after the onset of JIA. Their screening can last for 2 years only (Heiligenhaus et al., 2007).
8. Screening interval may be increased from 3 to 6 months or from 6 to 12 months after the first 4 years

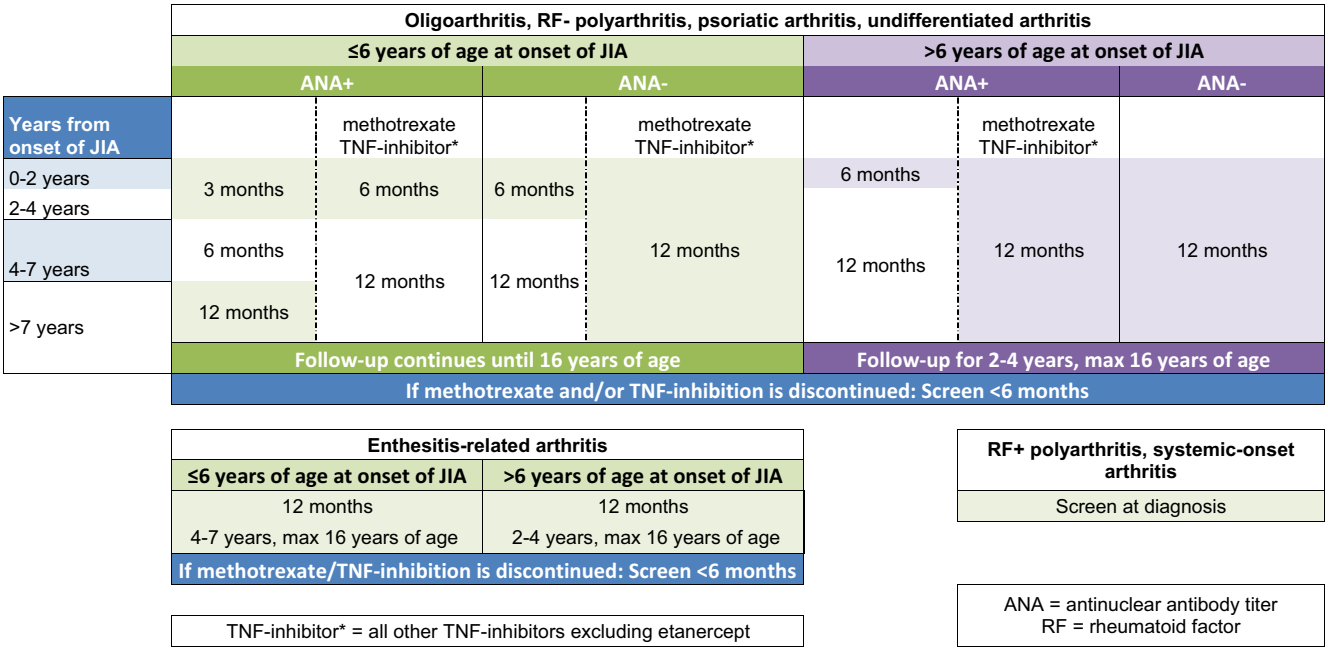


**FIGURE 1** Screening guideline for uveitis in juvenile idiopathic arthritis.

of follow-up if uveitis has not occurred (Heiligenhaus et al., 2007; Kotaniemi et al., 2001; Nordal et al., 2017; Rypdal et al., 2020).

9. Children receiving regular methotrexate, adalimumab or other monoclonal TNF-inhibitor treatment can be screened less frequently than children without such medication (Kostik et al., 2016; Papadopoulou et al., 2013; Tappeiner et al., 2016, 2018). If their antirheumatic treatment is irregular or discontinued, the risk of uveitis is likely to increase, and they should be screened more frequently.
10. Adults with JIA should be screened for uveitis if any ocular symptoms occur.

A page-long list of screening criteria is not practical in fast-paced clinical work. Therefore, a screening guideline in a table format has been used in Finland since 2014 (Leinonen, 2020). The guideline was updated in 2021 (Figure 1). The same screening guideline may be used in all Nordic countries, as the clinical picture of JIA is similar in them, except for a higher rate of uveitis in Finland (Nordal et al., 2017, Rypdal et al., 2020).

This screening guideline is intended as a clinical guide for planning suitable screening intervals for children with JIA and without a history of uveitis. It assesses the risk of developing JIA-uveitis based on the patient's subtype of JIA, ANA titre and age at onset of JIA, and their regular antirheumatic treatment. The higher the risk, the shorter the screening interval and the longer the total follow-up (Figure 1). Discretion may be used for children with onset of an ANA-positive high-risk JIA between 6 and 7 years of age, and they may be screened as frequently as children at highest risk of uveitis. This screening guideline differs from earlier recommendations because it considers methotrexate and monoclonal TNF inhibitors to be protective factors of JIA-uveitis (Angeles-Han et al., 2019; Heiligenhaus et al., 2007; Leinonen, 2020). However, if the child's antirheumatic treatment is variable, irregular or uncertain, it is safer to consider them 'without methotrexate or TNF-inhibition' in uveitis screening. This guideline also proposes a timeline for discontinuation of screening. If uveitis is diagnosed, this screening guideline no longer applies (Figure 1).

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