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Are you missing leukaemia?

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EDITORIAL

Missing a malignancy is a significant concern for paediatricians. It potentially leads to delay in treatment and impacts negatively on the doctor-patient/family relationship. Acute lymphoblastic leukaemia (ALL) is the commonest cancer in childhood affecting around 4 per 100,000 children per year. Brix *et al,* in this month's Archives, present a retrospective cohort of 286 patients with ALL diagnosed over two decades at two centres in Denmark.(1) They highlight the frequent presence of musculoskeletal (MSK) symptoms and signs amongst newly-diagnosed children, in particular 18.5% with localised joint pain of whom half had objective signs of arthritis. Other studies also suggest that MSK, and particularly joint, involvement is relatively common in ALL at around 10-20%. However, the probability of any given child presenting with MSK symptoms having ALL remains very low.(2) Only 10 of 1254 patients newly-referred to a Paediatric Rheumatology unit over a 10 year period had malignancy, of which 6 had ALL, representing 0.5%.(2) Another study reported 29 patients ultimately diagnosed with malignancy (13 leukaemias) referred to two North American Paediatric Rheumatology clinics over a 14 year period with a combined average new referral rate of 600/year, giving a leukaemia rate approximately 0.2%.(3) Key to management is the prompt and appropriate diagnosis and treatment by general paediatricians with referral to orthopaedics if features suggest a septic arthritis or osteomyelitis, to oncology if there are worries about malignancy or to paediatric rheumatology if there are concerns about inflammatory arthritis.

In the study by Brix *et al,* the group of 53 children with arthralgia and/or arthritis had a significantly longer delay in diagnosis (including parental, doctor and administrative factors) of 4 weeks compared with 2 weeks in those without joint involvement.(1) The median time from symptom onset to diagnosis of ALL in the subgroup with arthritis was 45 days. As the

authors suggest, the presence of objective arthritis is likely to lead clinicians along a diagnostic pathway towards reactive arthritis, juvenile idiopathic arthritis (JIA) or osteomyelitis. It is not possible to discern from the study at which stage the delay occurred: whether before initial presentation to health professionals or after first evaluation. Reassuringly, the long term follow-up data demonstrate that the group of ALL patients with joint involvement at presentation had significantly better event-free and overall 5-year survival compared with the group without. The latter, however, included a higher proportion of T cell ALL which had a poorer outcome during the 1992-2013 period and explains the significant difference in outcomes. It would be interesting for future studies to focus on ALL subtypes and leukaemia genetics: do certain forms present more commonly with joint symptoms which also have better survival outcomes?

What can be done to avoid misdiagnosis of children with arthralgia or arthritis? The first step is always to consider malignancy in the differential diagnosis and remain alert for clinical features which do not fit an expected pattern. More typical features of ALL such as fever, fatigue, bruising and bleeding must prompt further investigation, although this study highlights that constitutional features and bleeding were less common in the group with joint manifestations at presentation compared to those without (55% vs 81% and 10% vs 43% respectively).(1) The presence of non-articular musculoskeletal symptoms, particularly long bone and back pain, is unusual in reactive arthritis or JIA and raises the possibility of leukaemia or primary bone tumours. Any abnormalities of the full blood count warrant further investigation and a blood film can identify lymphoblasts, as was the case in 70% of children with ALL and joint involvement in the current study.

As with many areas of child health, no single clinical feature or investigation alone is sufficient to make a diagnosis. Recognising ALL presenting solely or predominantly with musculoskeletal symptoms can be difficult. The combination of low neutrophil count (<1 × 10^9/L), low haemoglobin (<10g/dL) and elevated LDH (>500IU/L) was associated with 93% sensitivity and 100% specificity in distinguishing a malignancy from JIA in a cohort of 134 patients presenting with MSK pain.(4) Another retrospective study concluded the combination of low white cell count (<4 × 10^9/L), low-normal platelet count (150-250 × 10^9/L) and history of night-time pain when present together had sensitivity of 100% and specificity of 85% for diagnosis of ALL compared with JIA.(5) These studies indicate that a full blood count (FBC) and LDH can be very valuable in recognising ALL. However, a significant proportion of children with ALL presenting with joint symptoms have a normal FBC: 24% in the study by Brix *et al.* The LDH was below the upper limit of normal in 37% of those with joint involvement.(1)

In the study published in this issue of Archives, 19% of the 27 ALL patients presenting with arthritis had >4 joints affected and could therefore mimic polyarticular JIA. The more typical features of ALL including fever, lymphadenopathy and hepatosplenomegaly associated with arthralgia/arthritis are very similar to the presentation of systemic JIA. In the majority of children with systemic JIA and a proportion of children with polyarticular JIA, systemic corticosteroids are part of the initial treatment. Potential harm could be caused to children with undiagnosed ALL if giving high-dose steroids precipitates tumour lysis syndrome and thwarts complete diagnostic work-up of the leukaemia. More worryingly, it could lead to partial treatment of the leukaemia followed by steroid-refractory relapse. For this reason, children suspected of having systemic JIA or those with a polyarticular presentation with any suggestion of constitutional symptoms or non-articular pain, any abnormalities with the FBC,

blood film, LDH or liver function tests should be discussed with haematology before commencing treatment. We suggest that the standard practice should be definitive investigation with diagnostic bone marrow aspiration in these select cases unless there is a strong reason not to do so.

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