Chest Radiographs for Distinguishing ADA-SCID from Other Forms of SCID

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Abstract

Purpose Early differentiation of adenosine deaminase deficient severe combined immunodeficiency (ADA-SCID) from other forms of SCID may initiate appropriate treatment interventions with the aim of metabolic detoxification and improved outcome. Our hypothesis was that previously described radiological features (inferior scapular angle squaring and spurring and costochondral cupping) can differentiate ADA-SCID from other forms of SCID.

Methods Chest radiographs at clinical presentation between 2000 and 2017 of children with ADA-SCID were retrospectively included, provided that the radiological features were assessable. Random chest radiographs of children with other forms of SCID were included for comparison. Three paediatric radiologists (2 senior, 1 junior) assessed the radiographs for the specific radiological features and stated their diagnosis (ADA-SCID or non-ADA-SCID). An optimal threshold for test performance was defined using a ROC curve.

Results Thirty-six patients with ADA-SCID and twenty-five patients with non-ADA-SCID were included (median age 3.8 months). The optimal threshold for test performance was at approximately < 7 months old: sensitivity 91.7%, specificity 80.7%, interreader agreement was k = 0.709, AUC 0.862. The positive likelihood ratio for scapular squaring, scapular spur, and costochondral cupping was 4.0, 54.6 and 7.8, respectively. The test was valid when performed by both senior and junior paediatric radiologists.

Conclusion Radiological features such as scapular spurring, scapular squaring and costochondral cupping can reliably differentiate between ADA-SCID and other forms of SCID. This is true for children aged approximately < 7 months, and this is reliable when assessed by both senior and junior paediatric radiologists.

Keywords Pediatric · ADA-SCID · SCID · radiograph · diagnosis · ERT · HSCT

Introduction

Severe combined immunodeficiency (SCID) consists of a heterogeneous group of inherited disorders characterized by lack of T cells and variable B and NK cell development resulting in severe dysfunction of the immune system. The clinical phenotype of SCID patients includes a spectrum of complex clinical presentations; however all share common features consisting of...
serious recurrent infections in the first few months of life and often failure to thrive and chronic diarrhoea [1].

SCID due to adenosine deaminase deficiency (ADA-SCID) is one of the more prevalent subtypes of SCID and accounts for 10–20% of all cases, with an estimated incidence of one per 0.2–1 million [2]. More than 70 pathogenic genetic variants have been identified in individuals with ADA deficiency [3]. The immunodeficiency is severe, presents in early life and is fatal if left untreated. Due to the defect in the purine metabolic pathway which leads to increased levels of the toxic metabolite dATP, ADA-SCID not only manifests itself as a systemic disorder which primarily affects lymphocyte viability and function, but also includes involvement of the lungs, bones, liver and neural system [4, 5]. Patients can present with a severe disorder which primarily affects lymphocyte viability and function, but also includes involvement of the lungs, bones, liver and neural system [4, 5]. Patients can present with a severe pneumonitis without an infectious organism being isolated [6] which may relate to impaired surfactant metabolism [7].

Initial management consists of aggressive treatment of underlying infections and supportive care. Enzyme replacement therapy (ERT) with pegylated ADA can stabilise patients prior to definitive therapy, allowing metabolic detoxification and often transient improvement in lymphopenia. Corrective treatment options include allogeneic haematopoietic stem cell transplantation (HSCT) with survival rates up to 86% for matched sibling donors [8] and more recently autologous ex vivo gene therapy [2, 9, 10].

Awareness of ADA-SCID associated skeletal abnormality may trigger prompt focused diagnostic investigations that would lead to early recognition of ADA deficiency in a child with suspected immunodeficiency. Early differentiation of ADA-SCID from other SCID may be particularly beneficial to pneumonitis where the implementation of ERT can lead to significant improvement [6, 9].

Various skeletal abnormalities associated with ADA-SCID have been described in case reports. The most prominent are squaring and spur formation of the inferior angle of the scapula and splaying and cupping of the costochondral junctions [11–13] (images 1, 2, 3). More subtle, less established skeletal abnormalities include thin metaphyseal sclerotic lines at the iliac apophyses, flattened vertebral bodies and mild metaphyseal changes of the long bones [12, 14]. Importantly, the described rib abnormalities have been reported to resolve after treatment [13]. ADA-SCID has a specific appearance on histology of the bones which normalises over time along with the radiological abnormalities, but whether this is due to treatment or natural progression is unclear [12, 14].

This study was designed to test the hypothesis that chest radiographs demonstrating inferior scapular angle squaring and spurring, in association with splaying and cupping of the costochondral junctions, may reliably distinguish ADA-SCID from other forms of SCID. Our primary aim was to assess the detection performance of paediatric radiologists, at both senior and junior levels, in a larger population than previously described whilst comparing them to a non-ADA-SCID control group. Secondly, as these skeletal abnormalities seem to disappear over time, when available, we also included follow-up chest radiographs to gain an understanding of when these features disappear.

**Methods**

This was a retrospective study performed in a tertiary immunology centre receiving SCID referrals. Local institutional approval was acquired, and the need for patient informed consent was waived.

Children with diagnoses of ADA-SCID confirmed between 2000 and 2017 were retrospectively identified. Their chest radiographs, performed at the time of clinical presentation, were evaluated by a paediatric radiologist (MV) for visibility of the inferior scapular angle. Children were included when at least one inferior scapular angle was properly visualised on the chest radiograph. The costochondral junctions were always sufficiently assessable. In addition, children with non-ADA-SCID were randomly selected by a member of the immunology team (VT). When suitable radiographs were available both at presentation and > 18 months, the later radiographs were also included to assess if the radiological features resolved.

Radiographs were anonymised and randomly presented to 3 radiologists (JA, AC, CO, with 2, 12 and 25 years of dedicated paediatric radiology experience, respectively). Only anterior-posterior (AP) views were available. Before scoring the radiographs, the radiologists were asked to study three papers which have previously reported on the radiological features of ADA-SCID [11–13]. The junior radiologist had been unfamiliar with reported ADA-SCID features. Next, the following radiological features were assessed for in the study population: squaring of the inferior scapular angle (yes/no), scapular spur (yes/no), cupping of costochondral junctions (yes/no) and ADA-SCID (yes/no). Radiologists assessed the radiographs independently and were blinded to patient history or other imaging. In case of discrepancies, no consensus meeting was held.

Statistical analysis consisted predominantly of description and test performance calculations. When available, follow-up radiographs at > 18 months were excluded for ADA-SCID detection test performance, separate radiological feature test performance and positive likelihood ratios. Statistics were performed using SPSS for Windows (release 22, IBM, New York, United States of America). The level of significance was set at \( p < 0.05 \). A receiver operating characteristics (ROC) curve was used to determine an optimal age threshold for the radiological features. Cohen’s kappa statistics was calculated to assess interreader agreement (\( \kappa \)) for ADA-SCID detection. Interreader agreement was classified as poor for \( \kappa < 0.00 \); slight for \( \kappa 0.00–0.20 \); fair for \( \kappa 0.21–0.40 \); moderate for \( \kappa 0.41–0.60 \); good for \( \kappa 0.61–0.80 \); and excellent for \( \kappa 0.81–1.00 \).
Results

78 children with ADA-SCID were retrospectively identified, and of these, 36 patients had chest radiographs that fulfilled the inclusion criteria (M:F 22:14, median age 3.1 months, IQR 10.7 months, Table 1). Specific mutations are described in Table 2. Next, 25 children with other forms of SCID were randomly included (M:F 15:10, median age 4.8 months, IQR 5.2 months, subtypes listed in Appendix Table 6). In 4 ADA-SCID and 4 non-ADA-SCID patients, radiographs were available both at presentation and > 18 months. The study flowchart is presented in Appendix Fig. 1.

Among the 36 ADA SCID patients, mutations were found in 34 patients (Table 2). Homozygous mutations were detected in 26 patients, compound heterozygous mutations were seen for 8 patients and 2 mutations were not identified. The most common mutation seen was Gly216Arg occurring in 16 patients (12 as homozygotes and 4 as compound heterozygotes). The second most observed mutation was Gln3* detected in 4 patients (3 homozygotes and 1 heterozygote). Because of the low number of patients per subtype, comparing dATP and ADA activity of genotypes to radiological performance was not statistically robust.

Average sensitivity for the detection of ADA-SCID, excluding the second radiographs if present, was 62.9% (mean amongst 3 radiologists: 22.6/36 patients), specificity 82.9% (20.7/25, Table 3). A ROC curve, performed for both senior radiologists, determined that for both radiologists the optimal trade-off between sensitivity and specificity was at age 7.3 months. The subgroup ≤7.3 months consisted of 24/36 ADA-SCID and 19/25 SCID patients, the subgroup > 7.3 months of the remaining 12/36 ADA-SCID and 6/25 SCID patients. For ≤7.3 months average sensitivity was 91.7% (22/24); specificity was 80.7% (15.3/19). > 7.3 months average sensitivity was 10.9% (1.3/12); specificity was 88.9% (5.3/6). For the whole cohort, the average area under the curve (AUC) was 0.728, for ≤7.3 months 0.862, and for > 7.3 months 0.472. Average interreader agreement, including second radiographs, for the whole cohort was κ 0.741 (good), κ 0.709 (good) for ≤7.3 months and κ 0.434 (moderate) for > 7.3 months (Table 4).

When comparing intra-patient chest radiographs at presentation to > 18 months, at presentation mean age for SCID patient (n = 4) was 9.7 months (SD 5.2) and 33.8 months (SD 12.5) at follow-up. For ADA-SCID patients (n = 4), mean age was 6.2 months (SD 6.1) at the initial radiographs and 31.2 (SD 8.1) at follow-up.

| Table 1 | Demographics of the whole cohort of included patients |
|---------|------------------------------------------------------|
|          | Number of patients | Age at clinical presentation (months), median (IQR) | M:F ratio |
| SCID     | 25              | 4.8 (5.2)            | 15:10      |
| ADA-SCID | 36              | 3.1 (10.7)           | 22:14      |
| Total    | 61              | 3.8 (8.2)            | 37:24      |

IQR Interquartile range

| Table 2 | Distribution of genetics within the included ADA-SCID subgroup |
|---------|---------------------------------------------------------------|
| Genetics (nucleotide) | Effect (amino acid) | Exon | Number of patients |
| Homozygous mutations (n = 26) | | | |
| c.646G > A | p.Gly216Arg | 7 | 12 |
| c.7C > T | p.Gln3* | 1 | 3 |
| c.1078-15 T > A | splicing | Intron 11-12 | 2 |
| c.716G > A | p.Gly239Asp | 8 | 2 |
| c.632G > A | p.Arg211His | 7 | 2 |
| c.320 T > C | p.Leu107Pro | 4 | 1 |
| c.556G > A | p.Glu186Lys | 6 | 1 |
| c.478 + 6 T > A | NA | skip exon 5 | 1 |
| c.385G > A | p.Val129Met | 5 | 1 |
| c.955_959delAAGAG | p.Glu319Glyfs*320 | 10 | 1 |
| Compound heterozygous mutations (n = 8) | | | |
| c.478 + 1 G > A and NA | Abnormal gene splicing and NA | Intron 5 and N/A | 1 |
| c.955_959delAAGAG and c.781-78G > T | p.Glu319Glyfs*320 and N/A | 10 and N/A | 1 |
| c.367del and c.955_959delAAGAG | p.Asp123Thrfs*132 and p.Glu319Glyfs*320 | 5 and 10 | 1 |
| c.467G > A and c.478 + 1 G > A | p.Arg156His and abnormal gene splicing | 5 and intron 5 | 1 |
| c.310C > A and c.646G > A | p.Pro104Thr and p.Gly216Arg | 4 and 7 | 1 |
| c.466C > T and c.646G > A | p.Arg156Cys and p.Gly216Arg | 5 and 7 | 1 |
| c.646G > A and c.956_960 del | p.Gly216Arg and p.Glu319Glyfs*320 | 7 and 10 | 1 |
| c.7 C > T and c.646G > A | p.Gln3* and p.Gly216Arg | 1 and 7 | 1 |
| Genetics not available | | | 2 |
| Total patients in the ADA-SCID cohort | | | 36 |
Within the SCID intra-patient comparison in one patient out of 3 radiologists (a senior radiologist) diagnosed ADA-SCID at 5.7 months, and subsequently as not ADA-SCID at 52.5 months. All other radiographs were diagnosed by all as non-ADA-SCID at both time points.

For ADA-SCID radiographs, in one case ADA-SCID diagnosis was unanimous at 1.4 months and not ADA-SCID at 41.8 months. In one case, ADA-SCID was not diagnosed at either 15.2 (a relatively late presentation, compound heterozygous c.478 + 1 G > A) or 30.2 months. In the third, there was unanimous ADA-SCID diagnosis at 3.2 months with still 1/3 radiologists (senior) diagnosing ADA-SCID at 30.6 months. The fourth case received a unanimous diagnosis of ADA-SCID both at 4.7 and 22.2 months.

The positive likelihood ratio of the separate radiological features at ≤ 7.3 months for all readers combined were: squaring of the inferior scapular angle 4.0, scapular spur 54.6 and cupping of costochondral junctions 7.8 (Table 5). The highest sensitivity was seen for squaring of the inferior scapular angle features (91.7%, 66/72 with datapoints from all radiologists combined). The highest specificity was shown for the scapular spur (98.2%, 56/57 datapoints) and cupping of costochondral junctions 89.5% (51/57 datapoints) (Table 5). A scapular spur was always seen in conjunction with squaring of the inferior scapular angle.

### Discussion

This study included two cohorts of patients with ADA-SCID or non-ADA-SCID whose chest radiographs were retrospectively assessed for radiological features that are associated with ADA-SCID. We tested the hypothesis that these previously reported skeletal features (squaring of the inferior scapular angle, a scapular spur and cupping of costochondral junctions) reliably distinguish ADA-SCID from other forms of SCID on chest radiographs. Our results show that this hypothesis is true for children ≤ 7.3 months. The high sensitivity and specificity of the test at ≤ 7.3 months (91.7% and 80.7% respectively) allows for a high rate of detection with a low rate of false positives when applied in the clinical setting of patients with immunodeficiency. When these radiographic features are present, this should lead to timely and specific investigation of ADA-SCID and early treatment such as enzyme replacement.

We also demonstrated that these features are reliable both for senior paediatric radiologists and for a junior paediatric radiologist with no prior knowledge of ADA-SCID when allowed to study the relevant literature. Lastly, we observed that the radiological features disappear around the 7th month of life after which these features can no longer be used to distinguish ADA-SCID from SCID.

The derived threshold significantly improved test performance for ADA-SCID detection for children ≤ 7.3 months old, whereas test performance became poor (sensitivity 10.9%, average AUC 0.472) in children over this age. This supports a previously reported finding that the radiological features disappear over time [11]. It should be noted that the threshold of 7.3 months is not a hard cut-off, and for clinical purposes, the disappearance of the features should be expected around 7 months. All patients underwent treatment for ADA-SCID which may relate to the disappearance of radiological features. However, this may not be the case for all patients, as

### Table 3 Test performance of ADA-SCID detection, given per reader and as the mean of all three readers

| Reader 1 (senior) | Sensitivity, (%) (n/all) | Specificity, (%) (n/all) |
|-------------------|-------------------------|-------------------------|
| Whole cohort      | 58.3 (21/36)            | 88 (22/25)              |
| < 7.3 months      | 87.5 (21/24)            | 89.5 (17/19)            |
| > 7.3 months      | 0 (0/12)                | 83.3 (5/6)              |
| Reader 2 (senior) | Whole cohort            | 66.7 (24/36)            | 84 (21/25)              |
| < 7.3 months      | 95.8 (23/24)            | 78.9 (15/19)            |
| > 7.3 months      | 8.3 (1/12)              | 100 (6/6)               |
| Reader 3 (junior) | Whole cohort            | 63.9 (23/36)            | 76 (19/25)              |
| < 7.3 months      | 91.7 (22/24)            | 73.7 (14/19)            |
| > 7.3 months      | 8.3 (1/12)              | 83.3 (5/6)              |
| Mean of all 3 radiologists | Whole cohort | 62.9 (22.6/36) | 82.9 (20.7/25) |
| < 7.3 months      | 91.7 (22/24)            | 80.7 (15.3/19)          |
| > 7.3 months      | 10.9 (1.3/12)           | 88.9 (5.3/6)            |

### Table 4 Interreader agreement of ADA-SCID detection within the whole cohort, given for each radiologist combination and as the mean

| Reader 1 and 2    | Kappa, whole cohort | Kappa, ≤ 7.3 months | Kappa, > 7.3 months |
|-------------------|---------------------|---------------------|---------------------|
|                   | 0.728 (p = 0.000)   | 0.716 (p = 0.000)   | 0.339 (p = 0.076)   |
| Reader 1 and 3    | 0.674 (p = 0.000)   | 0.602 (p = 0.000)   | 0.339 (p = 0.076)   |
| Reader 2 and 3    | 0.820 (p = 0.000)   | 0.811 (p = 0.000)   | 0.623 (p = 0.001)   |
| Mean              | 0.741               | 0.709               | 0.434               |

*
one of the follow-up chest radiographs of a patient with ADA-SCID received a unanimous ADA-SCID diagnosis both at 4.7 and 22.2 months, despite treatment. Therefore, a definitive explanation for the disappearance of these features is not yet clear.

Although we analysed the radiological features as separate variables, they are not independent of each other. The observation that a spur was never seen without squaring suggests that a spur is a more pronounced manifestation of the same underlying process. This hypothesis is supported by the test performances of squaring and spurring: although a spur is less sensitive (68.1% versus 91.7% respectively), specificity is higher (98.2% versus 77.2% respectively) and has a much higher positive likelihood ratio (54.6 versus 4.0 respectively).

We also note that the squaring and spurring of the inferior scapular angle apophysis are radiologically similar to the splaying and cupping of the costochondral junctions. Therefore we hypothesise that the underlying histopathology may be the same, and we suggest that the inferior angle of the scapula is a metaphyseal equivalent similar to the costochondral junction of the ribs. The spur may reflect the junction of membranous bone (presumed to be unaffected by ADA deficiency) with the abnormally ossified enchondral bone of the inferior angle apophysis. Why these sites show clear abnormalities not widely visible in other elements of the skeleton is not clear.

When inferior scapular angle squaring or spurring, or costochondral cupping are detected in a child, radiological differential diagnoses must be considered; the underlying growth plate disturbances of which could be the same as in ADA-SCID. Differential diagnoses include metaphyseal skeletal dysplasias such as cartilage hair hypoplasia, rickets and bone disease of prematurity. However the clinical presentation, immunophenotype and disease course is generally sufficiently different to distinguish them from ADA-SCID [12]. The histopathology of the ADA-SCID affected growth plate may also differ [12]. In rickets, the chondrocyte proliferation zone is present, but hypertrophic chondrocytes accumulate due to impaired normal apoptosis. [15, 16]. In ADA-SCID, the proliferation zone is absent with direct transition of resting chondrocytes into hypertrophic chondrocytes in resting cartilage with few osteoblasts and osteoclasts observed [12]. In addition, necrotic chondrocytes and large amounts of cellular debris have been reported [14]. We propose that the accumulation of dATP in ADA deficiency may have toxic effects on proliferating chondrocytes. The low number of osteoblasts and osteoclast has been linked to B-cell dysfunction inherent

| Table 5 | Test performance and likelihood ratio of separate radiological features for the detection of ADA-SCID in all patients ≤ 7.3 months, derived by combining datapoints from all radiologists* |
|-----------------|-----------------|-----------------|-----------------|
| Squaring of inferior scapular angle (n/all) | Scapular spur (n/all) | Cupping of costochondral junctions (n/all) |
| Sensitivity (%) | Specificity (%) | PLR |  |
| 91.7 (66/72) | 77.2 (44/57) | 4.0 |  |
| 68.1 (49/72) | 98.2 (56/57) | 54.6 |  |
| 81.9 (59/72) | 89.5 (51/57) | 7.8 |  |

* e.g. 24 patients * 1 datapoint/radiologist (n = 3) results in 72 total datapoints

Image 1 The chest radiograph on the left side (1a) of a 3-month old with ADA-SCID demonstrates scapular squaring and spurring (arrows) and splaying and cupping of the costochondral junctions (arrowheads). For comparison, on the right side (1b), a 4-month old with non-ADA-SCID with a normal inferior scapular angle (arrow) and normal costochondral junctions (arrowheads)
of ADA deficiency. The abnormal B-cell function results in abnormal adenosine receptor signalling which then causes decreased osteoclastogenesis and impaired osteoblast function and reduced bone formation \[4, 17\]. It should be noted that the abnormal growth plate histology in ADA-SCID were not seen in treated patients \[12, 14\].

This study suffers from several limitations. The first is its retrospective nature. As ADA-SCID is an ultra-rare condition, only a retrospective methodology was suitable to include sufficient patients within an acceptable timeframe. This did however mean that many chest radiographs were not suitable as the inferior scapular angle was not visible. It would have also been interesting to include radiographs of other bones (e.g. iliac wings, vertebral bodies and long bones) which were not available in sufficient numbers in our population.

The second limitation is the selection bias of our cohort. By only including ADA-SCID and SCID children, the value of the studied test is not proven in a less selected population. However, given the rarity of all SCID diagnoses, any test designed for such patients should be limited to a clinical scenario with a high pretest probability of SCID such as suspected immunodeficiency. A selection bias also involved the included chest radiographs. Only SCID children with respiratory involvement and HSCT work-up would have been included. Children who underwent multiple chest radiographs had a higher chance of having a chest radiograph with a visible inferior scapular angle, so it is likely their clinical condition was worse, requiring numerous x-rays; radiographic and skeletal changes may be more pronounced in sicker patients and therefore our results should be interpreted in this setting.

**Conclusions**

Radiological features of ADA-SCID such as squaring or spurring of the inferior scapular angle and cupping of the costochondral junctions are detected frequently in ADA-SCID patients younger than approximately 7 months of age. The presence or absence of these features can reliably distinguish ADA-SCID patients from other forms of SCID. Recognition of these radiological features should trigger focused diagnostic investigations leading to early recognition of ADA deficiency in a child with suspected immunodeficiency. The test is not only valid when performed by senior paediatric radiologists but also by junior paediatric radiologists after studying the relevant literature. We hypothesise that the radiological features of the scapular angle are the same as the costochondral junctions because the inferior scapular angle...
apophysis acts as a metaphyseal equivalent. The features disappear after approximately 7 months of age.

Acknowledgements All research at Great Ormond Street Hospital NHS Foundation Trust and UCL Great Ormond Street Institute of Child Health is made possible by the NIHR Great Ormond Street Hospital Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Appendix 1

Table 6 Distribution of SCID subtypes within the included non-ADA-SCID subgroup

| Subtype                                         | Number of patients |
|-------------------------------------------------|--------------------|
| Gamma-chain deficiency (X-linked SCID)          | 5                  |
| RAG1 deficiency                                 | 3                  |
| RAG2 deficiency                                 | 1                  |
| IL7Ra receptor deficiency                       | 3                  |
| JAK3 deficiency                                 | 2                  |
| T-cell lymphopenia                              | 3                  |
| T-B + NK +/- SCID                               | 1                  |
| DNA ligase 1 deficiency                         | 1                  |
| Athymic CHARGE syndrome (CDH7)                  | 1                  |
| Undefined genetics                              | 5                  |
| Total patients in the non-ADA-SCID cohort       | 25                 |

Appendix 2

Fig. 1 Study flowchart

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.
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