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Incidental findings in surveillance of paediatric Li Fraumeni patients – A single centre experience

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ABSTRACT

Li-Fraumeni syndrome (LFS) is a rare cancer predisposition syndrome. Patients with LFS are at increased risk of early-onset tumours and undergo intensive radiological imaging surveillance to improve the early identification of malignancies. This report of a single-centre experience has shown that through surveillance imaging, especially whole-body MRIs, there is a high incidence of incidental findings. Incidental findings can result in anxiety and further evaluation often in the form of radiological imaging. It is important that patients and families are clearly counselled about incidental findings and findings of unknown clinical significance when undergoing imaging as part of a surveillance programme.

Introduction

Li-Fraumeni syndrome (LFS) is a cancer predisposition syndrome caused by constitutional pathogenic variants in the *TP53* gene [1].

LFS is characterised by a high and early onset cancer risk. The tumour spectrum is wide and includes soft-tissue sarcoma, osteosarcoma, adrenocortical carcinoma, central nervous system tumours, leukaemia and breast cancer.

Current United Kingdom guidelines advise that paediatric patients with LFS should undergo abdominal ultrasound (USS) every three to four months, annual whole-body Magnetic Resonance Imaging (WB-MRI) and annual brain MRI from the first year of life [2].

This analysis describes a single-centre experience of surveillance screening in children with LFS in the All Wales Paediatric Cancer Predisposition clinic.

Methods

Electronic records of all patients with a pathogenic, likely pathogenic TP53 variant or suspected diagnosis of LFS, based on family history, were retrospectively reviewed. These patients were all seen in the Welsh Paediatric Cancer Predisposition Service, since its establishment in 2020. This analysis includes all children known to have a diagnosis of Li Fraumeni syndrome undergoing surveillance in Wales.

The number and nature of incidental findings on surveillance WB-MRI, brain MRI and abdominal USS performed were identified, as were the findings of any resulting investigations or imaging.

Results

Nine patients under the age of eighteen had suspected or confirmed LFS. There were six females (66 %) and three males (33 %), with ages ranging between three years and eighteen years.

Seven had a pathogenic or likely pathogenic variant in *TP53*. Two siblings, one of whom developed a choroid plexus tumour at five months and the other an epithelioid sarcoma at nine years, but in whom no germline TP53 pathogenic variant was detected, were offered screening. This was following multi-disciplinary team discussion, despite their

Abbreviations: LFS, Li Fraumeni Syndrome; MRI, Magnetic Resonance Imaging; USS, Ultrasound Scan; WB-MRI, Whole Body Magnetic Resonance Imaging.

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family history not meeting classic LFS criteria [3].

Twenty-three WB-MRIs were performed, with each patient having between two and three WB-MRIs. Thirteen of those WB-MRIs had incidental findings, with sixteen incidental findings in total. 43.8 % (7/16) of incidental findings were identified on first surveillance WB-MRI imaging.

Twenty-nine brain MRIs were performed, with each patient having between two and five brain MRIs. Of those brain MRIs, two had incidental findings.

Table 1 lists the incidental findings noted on MRI, the further evaluation that was advised by the reporting radiologist and the outcome of the further imaging (Fig. 1).

Seventy-eight abdominal USS were performed on patients with confirmed or suspected LFS. All patients had between four and twelve abdominal USS. Only two abdominal USS identified incidental findings. The incidental findings were a small (diameter 9 mm) benign renal cyst. Due to the frequency of abdominal USS imaging in the surveillance protocol, this finding did not result in any further imaging than already planned. A focal lesion in the left lobe of the liver was also identified. This had been noted on the WBMRI, resulting in an MRI Liver with contrast being requested.

Following on from the incidental findings on WBMRI, MRI Head and USS imaging, no significant pathology was detected in the recommended further radiological investigations. Also, of note, all incidental findings were unchanged or resolved on further MRI imaging.

Conclusion

This single centre experience demonstrates that the majority of WBMRI scans (56 %) have identified incidental findings as part of the LFS surveillance programme. Though limited by patient numbers, most patients included in this review had incidental findings, on LFS surveillance imaging, which were later confirmed to be benign or normal variants.

Pathogenic TP53 variant carriers may have a higher rate of benign lesions, such as bone or renal cysts, than the general population [4]. Ballinger et al. [5] and Mai et al. [6] showed false-positive rates of 43 % (173 patients) and 29.6 % (116 patients) respectively on WB-MRI in a mixed adult and paediatric population with LFS. This compares with 26.8 % of paediatric patients, referred to a musculoskeletal oncology centre, having incidental findings on WB-MRI [6]. Saya et al. [4] reported a higher incidence of incidental findings, in adults with pathogenic TP53 variants, on baseline WB-MRI compared with a control population.

WBMRI is usually used for musculoskeletal surveillance for a number of conditions including Osteosarcoma and Langerhans Cell Histiocytosis. LFS is a relatively new indication for WBMRI and therefore many paediatric radiologists may have limited experience in reporting these scans. This variation in experience may result in under or over-reporting of lesions which may be of limited or unknown clinical significance [7]. It has been suggested that the use of WBMRI could be improved by strict interpretation and reporting guidelines to compensate for false-positives [8].

It is important to consider the psychological effects of cancer surveillance programmes in children and young people. Regular surveillance over many years can impact patients and families emotionally [9]. Bauml et al., 2016 described the concept of “scanxiety”, an anxiety associated with imaging and waiting for imaging results that is prevalent amongst patients having surveillance imaging or imaging of solid tumour oncology [10].

The additional burden of further testing to evaluate incidental findings is likely to contribute to the negative psychological impact of incidental findings. This additional burden may include extra radiation if Computerised Tomography or X-Ray are needed to further evaluate findings [8,11].

As a result of these findings, there is now a greater focus to ensure

Table 1
Incidental findings on MRI, further evaluation required and outcome.

Incidental finding from Brain MRI CNS	**Further evaluation**	**Outcome**
Small left middle cranial fossa arachnoid cyst (unchanged from previous imaging).	No further imaging required	-
Chiari type I malformation.	No further imaging required	-
Incidental finding from Whole Body MRI	**Further evaluation**	**Outcome**
Musculoskeletal		
At C5/6, a paracentral disc osteophyte bar is causing indentation of the cord.	MRI & CT C-Spine	Confirms appearances of benign osteophyte. There are no associated sinister features.
Simple cyst arising from the right proximal tibiofibular joint.	No further imaging required	-
A well-defined T2 hyperintensive focus expanding the cortex of the right humeral metaphysis.	X-Ray Humerus	Appearances consistent with a fibrous cortical defect.
A focal abnormality in the upper thoracic vertebrae with T2 hyperintensity affecting the right side of the vertebral body, measures 9 mm.	MRI Spine	The well-defined lesion in the right hemivertebrae of T3 represents an atypical haemangioma.
Advanced wasting throughout right foot intrinsic muscles. Increased T2 signal in the head of the right first metatarsal and the phalanges of the right great toe. Similar appearances to left hallux.	Consider X-Ray both feet	No further imaging after clinical assessment.
The right patella is dislocated laterally. There is a large knee joint effusion which has increased in volume since the MRI in September.	No further imaging required	-
Genitourinary		
The right kidney mid pole T2 high signal intensity lesion measures 18 mm and is likely to represent a focal calyceal dilatation. There is prominence of the right pelvicalyceal system. The urinary bladder is significantly distended.	Routine USS as already planned	Right simple, renal cyst with stable appearances.
Small high T2 signal lesion within the mid pole of the right kidney, likely represents a small cyst.	Routine USS as already planned	Normal USS.
There are at least 4 focal T2 hyperintense lesions in the cortex of the right kidney. They are too small to discern on DWI sequences. No renal lesions on recent ultrasound.	Routine USS as already planned	Normal USS.
Mixed density structure in the right side of the lower pelvis with evidence of a fluid level. Most likely a haemorrhagic right ovarian cyst measuring 3.7 × 3.1 cm.	USS Pelvis	Ovarian cyst resolved.
There is a 7 mm T2 hyperintense focus in the left hemiscrotum. This is most likely to represent a benign epididymal cyst.	No further imaging required	-
Others		
Small focus of high signal intensity at the medial end of the left clavicle which appears	USS Neck	No detectable abnormality.

(*continued on next page*)

Table 1 (*continued*)

Incidental finding from Brain MRI CNS	Further evaluation	Outcome
to be in the root of the left neck/left supraclavicular fossa rather than in bone.		
Possible thrombus in the Left Internal Jugular Vein.	Doppler USS of neck veins	No evidence of acute thrombus.
Possible tiny focus within the apical segment of the left lower lobe.	CT Thorax	Small calcified nodule of uncertain significance. Stable on subsequent imaging therefore presumed benign.
Well-defined 15 mm T2 hyperintense focus in the medial aspect of the right breast. This may represent a lesion or focal fat within the developing glandular tissue.	USS Breast	No breast lesion identified.
There is a rounded focus of restricted diffusion in the left lobe of the liver which measures 18 mm. There is no anatomical correlate on T2 sequences.	MRI Liver with contrast	Lesion consistent with focal nodular hyperplasia. Stable on subsequent imaging.

MRI – Magnetic Resonance Imaging, CNS – Central Nervous System, CT – Computed Tomography, C-Spine – Cervical Spine, USS – Ultrasound Scan

patients are appropriately counselled regarding the potential of incidental findings on imaging.

Though the incidental findings identified were benign or normal variants, with increasing identification of patients with LFS and increasing surveillance imaging, there are likely to be findings of unknown clinical significance. These are also likely to result in additional psychological burden for the patient and families [10].

Until now, no formal patient-reported outcome or experience data has been collected to quantify the psychological distress caused in this cohort. Findings of a service evaluation identified that although patients and families see the benefit of surveillance, they describe the incidental findings and subsequent investigations causing anxiety. Further research is this area is required to understand the patient and family experience of Li Fraumeni syndrome surveillance.

There is no evidence of the published cost-effectiveness of Li Fraumeni radiological screening in the UK or European population. Tak et al., 2019 proved a 98 % probability that surveillance was the most cost-effective strategy for early cancer detection in patients with LFS using a willingness to pay threshold of $100 000 [12]. However, further imaging requirements due to incidental findings would result in increased financial cost and affect the overall cost effectiveness of the screening programme.

Further research is required to evaluate the rate of incidental findings in surveillance imaging of paediatric patients with LFS in order to better prepare patients and their families for the potential findings and further investigations.

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Ethics statement

This was a retrospective analysis of a routine clinical service and therefore no ethical approval was needed.

Statement of contribution

All authors have significantly contributed to the manuscript and have reviewed and agreed upon the manuscript content.

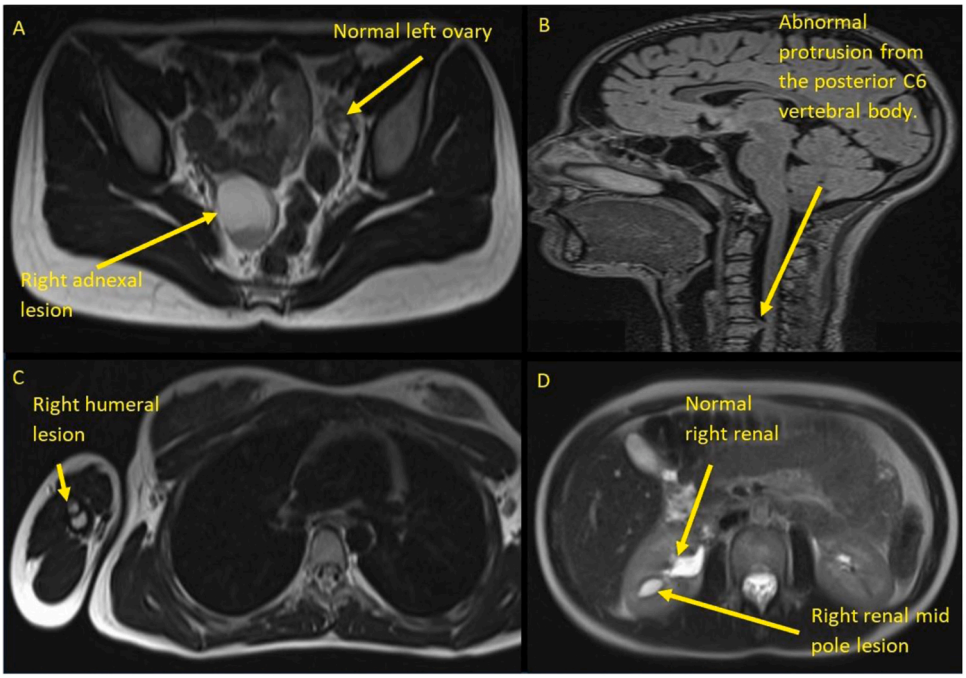

Fig. 1. Incidental findings on MRI. A) T2 weighted MRI, axial section. Demonstrates 3.7 cm predominantly high T2 signal cystic structure in the right adnexa with lower signal material layered posteriorly within this, creating a fluid-fluid level. Right ovary not seen separately. Felt most likely to be a haemorrhagic right ovarian cyst. B) T2 fluid attenuated MRI, sagittal section. Performed as part of the initial screening MRI head. Demonstrates posterior protrusion at C5/6 felt to represent a disc osteophyte bar with indentation of the ventral cord. C) T2 weighted MRI, axial section. Demonstrates a well-defined T2 hyperintensive focus centred upon and expanding the cortex of the right humeral metaphysis over multiple axial sections. D) T2 weighted MRI, axial section. Demonstrates 18 mm right renal mid pole lesion of homogenous T2 hyperintensity. No evidence of diffusion restriction. Most in keeping with a small renal cyst.

CRediT authorship contribution statement

Adams Madeleine: Writing – review & editing, Supervision, Conceptualization. **Isaac Rhian:** Writing – review & editing, Visualization, Formal analysis, Data curation. **Davies Mark:** Writing – review & editing, Supervision, Conceptualization. **Conti Hector:** Writing – review & editing, Conceptualization. **Nicholls Zoe:** Writing – review & editing, Visualization, Formal analysis, Data curation. **McVittie Elizabeth:** Visualization, Methodology, Formal analysis, Data curation, Investigation. **Alcock Amy:** Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Data availability

There is no shared data available.

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