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DICER1 syndrome and its various paediatric presentations: Case series and review of the literature

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ABSTRACT

DICER1 syndrome is a rare tumour predisposition syndrome, associated with a range of benign and malignant tumours, which may occur during childhood. A high index of suspicion is required to ensure appropriate diagnosis and testing, with early treatment and surveillance of at-risk individuals. In this report, we present 5 patients with variants in *DICER1* identified following diagnosis of a minimally invasive thyroid follicular cell carcinoma, a pineoblastoma, a pleuropulmonary blastoma, a urethral rhabdomyosarcoma and on sibling testing. Each of these children have presented at a young age, and 2 have presented with characteristic tumours prior to the ages currently recommended for initiation of routine screening. We discuss their presentation, management and follow up, as well as a review of the current literature on each associated tumour in relation to our patients. Overall, we demonstrate that DICER1 is a heterogenous condition and that there is a need for cascade testing of family members as well as regular screening for tumour development in affected children, although consideration should be made regarding initiating this screening at an earlier age depending on clinical findings.

1. Introduction

DICER1 syndrome, or pleuropulmonary blastoma familial tumour susceptibility syndrome [1], is a rare tumour predisposition disorder, with affected individuals having a variant of the *DICER1* gene (OMIM #606241), which may result in the development of benign and malignant tumours [2]. The commonest observed tumour in DICER1 syndrome is pleuropulmonary blastoma, typically occurring in younger children, with a peak incidence at the age of 8 months [2]. Thyroid involvement and ovarian sex cord-stromal tumours are also well reported in DICER1 syndrome. Although reported less frequently, Hodgkin Lymphoma, pineoblastoma, Wilms tumour and neuroblastoma have also been associated with pathogenic germline *DICER1* variants. We report 5 differing presentations of paediatric patients with DICER1 syndrome (Table 1) and discuss their management. Written informed consent was received from each patient prior to publication.

2. Cases

2.1. Child 1 and Child 2

A 3-year-old girl was under review due to an incidental finding of a renal cyst. During a routine clinic she was noted to have a palpable thyroid mass. Examination was otherwise unremarkable. There was a significant family history of thyroid disease-her mother had undergone a thyroidectomy due to a multi-nodular goitre (MNG) and was on thyroid replacement therapy. Several maternal female relatives also had MNG and had undergone partial or complete thyroidectomies, as well as the mother's maternal aunt having died from a 'brain tumour' (additional details not available) aged 30 years.

Thyroid function tests, parathyroid hormone and thyroid antibodies were normal, as were baseline haematological and biochemical indices. Thyroid ultrasound scan demonstrated a large vascular mass within the left lobe. MRI confirmed a 2.5×2.5×3.2 cm thyroid lesion with mass effect causing tracheal deviation (Fig. 1).

Following multidisciplinary (MDT) discussion, a hemi-

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Table 1
Summary of cases.

Case	Age at presentation (yrs)	DICER1 variant	Presentation
1	3	NM_177438.3: c.4110_4153del44;p.(Val1371Cysfs*11)	Minimally invasive thyroid follicular carcinoma
2	4	NM_177438.3: c.4110_4153del44;p.(Val1371Cysfs*11)	Thyroid nodules
3	15	NM_177438.3: c.4309_4312del;p.(Asp1437Metfs*16)	Pineoblastoma Thyroid cysts
4	2	NM_177438.3: c.5424 G>A;p.(Met1808Ile) NM_177438.3.c.4093del p.(Leu1365Tyrfs*14)	Pleuropulmonary blastoma
5	0.1	NM_177438.3: c.459 T>G; p.(Tyr153*)	Urethral embryonal rhabdomyosarcoma

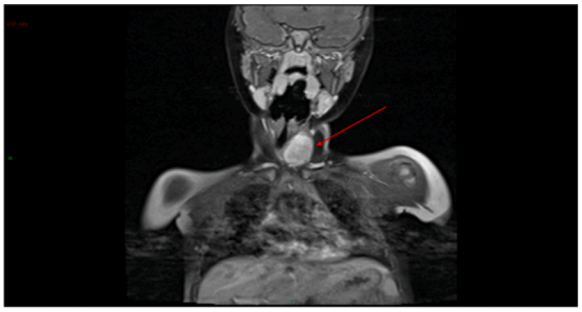

Fig. 1. MRI scan demonstrating thyroid lesion with tracheal deviation in Child 1.

thyroidectomy was performed. On histology, sections of left lobe of the thyroid demonstrated discrete tumour comprising of small follicles with areas of thick colloid. Cytologically, the majority of the cells had a coarse pattern within their nuclei with moderate amounts of eosinophilic cytoplasm. The tumour was positive for CAM5.2, A1/3 and TTF1. These findings were consistent with a diagnosis of minimally invasive follicular carcinoma. Excision of the left lobe of the thyroid was complete.

Subsequent genetic testing demonstrated our patient has a heterozygous *DICER1* pathogenic variant (Table 1). Cascade testing of her sibling (Child 2) revealed that she has the same mutation as her mother and one of her maternal aunts. Child 1 is now over three years post-surgical excision and remains clinically well and the renal cyst is stable.

Both children are followed up at six monthly intervals with abdominal ultrasound scans, chest X-rays and annual brain MRIs. On routine surveillance, both girls have incidental pineal cysts which remain stable. Case 2, currently aged 4 years, has recently been found to also have thyroid nodules on routine USS and remains under close follow up.

2.2. Child 3

A previously healthy 15-year-old girl presented with a short history of headaches and visual disturbance. She was noted by a local optician to have papilloedema and proceeded to have an urgent MRI which demonstrated a pineal lesion (2.9 cm×2.7 cm×2.5 cm) and hydrocephalus (Fig. 2). She had a complete resection and external ventricular drain (EVD) insertion.

Histological features were in keeping with a pineal parenchymal tumour (WHO grade IV). She was treated as per Children's Cancer and Leukaemia Group (CCLG) guidelines with St Jude's protocol with surgery, radiotherapy and 4 cycles of sequential high dose chemotherapy with autologous stem cell return. She is now 3 years post treatment and remains clinically well with no disease recurrence.

MRI spine, performed routinely as part of her staging investigations, demonstrated several cystic changes within the thyroid gland (Fig. 2). On ultrasound, multiple thyroid cysts within the left thyroid lobe were demonstrated. Given the diagnosis of pineoblastoma and identification of thyroid cysts, *DICER1* mutation analysis was performed (Table 1). On further questioning, it became apparent that there was a family history on paternal side of thyroid "problems." Her mutation was not inherited from her mother, but it has not yet been possible to test her father.

2.3. Child 4

A previously healthy 2-year-old girl presented with a 4 week history of respiratory symptoms suggestive of a respiratory illness. She was noted on examination to have reduced air entry throughout her right lung field. Chest X-ray demonstrated a large mass extending throughout her right lung field. Given a deterioration in her clinical condition, with a need for increasing respiratory support, she proceeded to have chest imaging which demonstrated a large tumour extending throughout her right lung field. This was biopsied and histology was suggestive of either

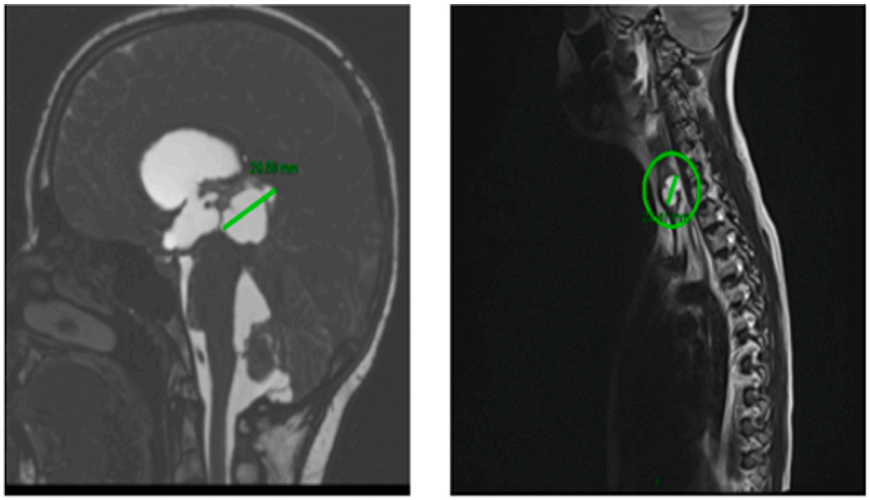

Fig. 2. MRI demonstrating pineal gland lesion and spinal imaging demonstrated cystic changes within the thyroid gland in Child 3.

a sarcomatous lesion or a pleuropulmonary blastoma.

Further deterioration prompted referral to paediatric intensive care for consideration of extracorporeal membrane oxygenation (ECMO) support. Repeat CT chest demonstrated increasing size of the lung lesion (Fig. 3).

Considering the results from a previous biopsy that suggested a malignancy, she received vincristine and actinomycin chemotherapy as per the RMS 05 protocol. Unfortunately, she rapidly deteriorated. Following extensive multidisciplinary team discussion, right lung tumour debulking was performed. Pathology confirmed a pleuropulmonary blastoma. Sadly, despite the best efforts of the team, our patient died shortly afterwards.

Genetic analysis on the tumour sample confirmed a pathogenic *DICER1* variant and a *DICER 1* variant of unknown clinical significance (Table 1). The patient's father was treated for a pineoblastoma in childhood. Germline testing has not been possible as no sample is available and the patient is deceased.

2.4. Child 5

A 3 week old baby, who was born at term via spontaneous vaginal delivery with no complications presented with a lesion at the tip of his penis. He was able to pass urine but examination under anaesthetic revealed a 2×0.5×1 cm pedunculated polyp with bruised appearance emanating from the urethral meatus (Fig. 4). Cystoscopy confirmed anterior urethral origin of the polyp, approximately 10 mm from the meatus. Histopathological analysis of the polyp demonstrated a translocation negative urethral embryonal rhabdomyosarcoma. Investigations did not reveal any distant metastatic disease. He had a tumour resection at 4 months of age and commenced chemotherapy with vincristine, actinomycin and cyclophosphamide followed by cycles of ifosamide, vincristine and actinomycin as per the rhabdomyosarcoma FAR-RMS trial IVA protocol. Genetic testing revealed a heterozygous pathogenic sequence variant (Table 1). He is currently 1 year post diagnosis and is progressing well.

3. Discussion

DICER1 syndrome is a cancer predisposition syndrome resulting from germline heterozygous pathogenic variants of the *DICER1* gene, which can lead to development of benign and malignant tumours in approximately a third of affected individuals [2].

The exact prevalence of DICER1 syndrome in unknown, although screening of germline whole exome sequence datasets suggests this may be 1:10,600 [3]. The majority of cases result from a germline mutation in the *DICER1* gene, some of which have occurred as a de novo event, but most are inherited in an autosomal dominant pattern with variable penetrance [4]. The *DICER1* gene is located on chromosome 14q32.13 and encodes endoribonuclease dicer, which plays a key role in the micro RNA processing pathway [5]. Mutations affect *DICER1* function, disrupting microRNA regulation and the expression of multiple other genes, leading to an increased risk of tumour development. It is reported that 5.3 % of patients who are *DICER1* carriers will have developed a malignancy by the age of 10, increasing to 19.3 % when 50 years [6].

Pleuropulmonary blastoma and Sertoli- Leydig cell tumours are the characteristic tumours associated with DICER1 syndrome. Presentation is variable, usually in individuals <40 years of age [7], and diagnosis requires a high index of suspicion.

3.1. Thyroid involvement

DICER1 plays a key role in normal development and hormone synthesis of the thyroid gland. Mutations of *DICER1* can therefore result in abnormalities within the thyroid, ranging from benign (MNG) to malignant thyroid disease. MNG is unusual in children and diagnosis of MNG, and a family history, should particularly raise suspicion of DICER1 syndrome [8]. In total, 32 % of women and 13 % of men with a *DICER1* variant will develop MNG by the age of 20 years, with this increasing to 75 % of women and 17 % of men by 40 years of age [9]. To date, the reason for this sex difference remains unknown.

Regarding malignant thyroid tumours, follicular adenomas and differentiated thyroid carcinoma (DTC) are associated with DICER1 syndrome. DTCs tend to follow an indolent course, with no deaths reported to date amongst patients with a *DICER1* mutation and a DTC [9]. The presence of a *DICER1* associated condition significantly increases an individual's risk of thyroid cancer, by 16–24 fold [10]. Individuals with a pleuropulmonary blastoma are at an increased risk of *DICER1* associated DTC. This risk is reported to be secondary to prior chemotherapy treatment and / or radiation exposure [11].

3.2. Pineoblastoma

Malignant tumours within the pineal gland are rare. Pineoblastomas are the second commonest pineal gland tumours and have historically been associated with germline mutations within the RB-1 gene, known as "trilateral" retinoblastoma. Recently, de Kock et al. have reported *DICER1* as also being implemented in the development of pineoblastoma [12]. Unlike other *DICER1* associated tumours where a missense mutation in the second allele is usually seen in RNase IIIb domain, *DICER1* related pineoblastomas have been reported to exhibit complete loss of

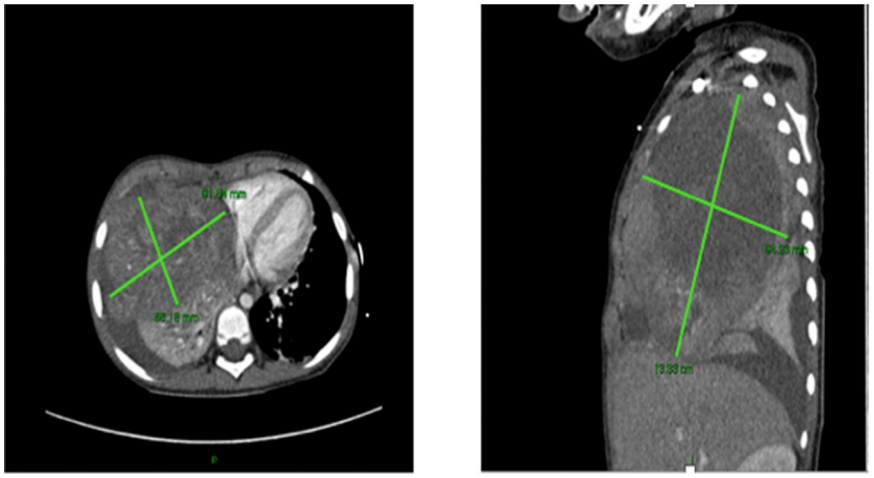

Fig. 3. CT chest demonstrating a large right hemithorax mass, measuring 13×8x9cm, with two distinct components to the mass in Child 4. Overall mass effect resulted in moderate right to left mediastinal shift.

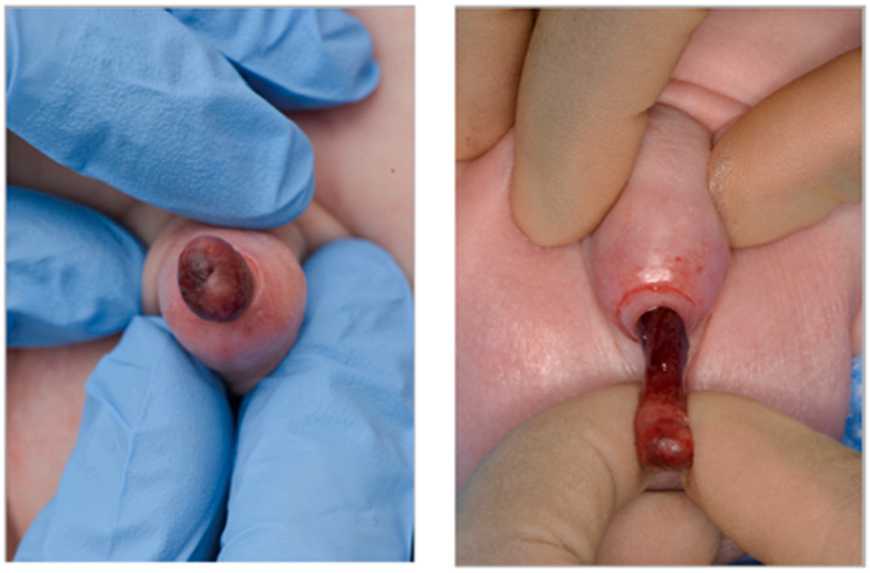

Fig. 4. Medical photography of penile urethral lesion in Child 5.

DICER1, with either loss of function (LOF) or loss of heterozygosity (LOH) [12]. Pineoblastoma, associated with RB1 alterations usually affects younger children who have a poor five-year overall survival (28.6–37.5 %), whereas loss of function alterations in *DICER1* tend to occur in older children with improved five-year overall survival (68–100 %) [13]. Current treatment for paediatric pineoblastoma in the UK consists of surgery, radiotherapy, high dose chemotherapy and sequential autologous stem cell transplant. It is recognised that patients over 4 years of age have a better overall survival and progression free survival than those under 4 years of age [14].

3.3. Pleuropulmonary blastoma

Pleuropulmonary blastoma (PPB) is a rare tumour of the lungs, occurring in children, usually <7 years [15]. Although rare, it is the commonest primary paediatric lung malignancy. It was the first tumour described in association with *DICER1*, and diagnosis should prompt genetic testing for *DICER1* mutations.

In patients with a diagnosis of pleuropulmonary blastoma, >70 % are due to germline mutations, of which the majority are inherited but 10–20 % arise due to de novo germline mutations [4]. The remainder are somatic mutations.

3.4. Rhabdomyosarcoma

Genitourinary embryonal rhabdomyosarcoma is the second most common form of rhabdomyosarcoma in children and is most commonly identified in the ovaries and vagina in girls, and the urinary tract in boys [16], although less common forms have been identified elsewhere [17].

3.5. Identification and surveillance

Recommendations for diagnosis of at risk individuals and ongoing surveillance strategies have been published, with emphasis being given to those <7 years, given the higher risk of PPB in this age group [4]. Given the incomplete penetrance of the *DICER1* mutation, we should not exclude *DICER1* syndrome in patients without a family history of *DICER1* associated tumours [6]. A high index of clinical suspicion is necessary to ensure that genetic testing is undertaken in those who present with typical tumours or with a family history of typical tumours. Of course, consideration should be given to the ethical implications of testing of asymptomatic family members. Should patients at risk of *DICER1* syndrome decline genetic testing, then clinical and radiological surveillance should still be encouraged [4].

Early recognition of tumours is associated with increased chance of cure, with most tumours being amenable to surgical resection if detected early. Current recommendations for children with *DICER1* variants are summarised in Table 2 [4,18]. Overall, recommendations suggest that children who are carriers of *DICER1* pathogenic variants should be

Table 2
Summary of recommendations for screening as per *(Bakhuizen et al. 2021) and **(Schultz et al. 2018).

Site / organ	Imaging / follow up recommended	Age of follow up according to SIOPE HGWG
Lungs (identification of pleuropulmonary blastoma)	Chest X-ray Chest CT	At birth (for those at risk) Biannual chest XR from birth until 7 years, or 6 years* Annual chest XR until 12 years ** Between 3 and 6 months Repeat CT at 2.5–3 years
Abdomen (identification of Wilms tumour cystic nephroma)	Abdominal ultrasound	Ultrasound every 6 months until 8 years, or 6 years* Annual ultrasound scan until 12 years**
Pelvis (identification of gynaecological tumours)	Pelvic ultrasound Alpha-fetoprotein (AFP)	6–12 monthly pelvic ultrasound from 8 years until at least 40 years
Thyroid (identification of follicular cell carcinoma)	Examination of thyroid and thyroid function tests (TFTs) Thyroid ultrasound scan	At each clinic visit From 8 years old, with scanning at 3 yearly intervals**
Cranial imaging (identification of pineoblastoma)	MRI head	Urgently if any CNS symptoms or signs Not routinely recommended but low threshold to image if clinical concerns.
Ophthalmology assessment (identification of ciliary body medulloepithelioma (CBME))	Dilated detailed ophthalmology assessment Visual acuity screening	Annually from 3 years until at least 10 years of age**

reviewed by a paediatric oncologist until they are 8 years old, with paediatric endocrinologists following them up after the age of 8 years, as the primary reason for follow up beyond this age is for thyroid assessment [18]. Although differences exist within the recommendations, there is an emphasis on the need to highlight the importance of patient and parent education about signs and symptoms which may be associated with typical *DICER1* associated tumours to prompt medical review and assessment.

Of note, currently, assessment of thyroid by ultrasound is recommended from 8 years, or earlier should the patient experience any thyroid related symptoms [18]. Scanning at 3 yearly intervals has been deemed reasonable, given the indolent nature of *DICER1* associated thyroid malignancies. However, 2 of our patients have had thyroid lesions, including one with having minimally invasive follicular carcinoma, much earlier than the recommended age of screening, so a cautious approach should be adopted. As with all *DICER1* associated tumours, parents and patients should be counselled about signs and symptoms to monitor for, and earlier assessment should be initiated as highlighted by our case series.

In summary, we present 5 children with *DICER1* mutations with different clinical courses and presentations. Two had *DICER1* associated thyroid disease under the age 4 years, highlighting the need to cautiously consider earlier surveillance imaging, if there is clinical suspicion or abnormal thyroid examination. When children present with *DICER1* associated tumours, a thorough family history should be obtained. Consideration should be given to the possibility of DICER1 syndrome and the need for regular review in accordance with published recommendations [4,18]. Implications of testing for other family members should also be recognised with genetic counselling and support available.

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Milind Ronghe: Writing – review & editing, Writing – original draft, Supervision, Formal analysis, Data curation, Conceptualization. **Courtney L Willis:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Angela K Lucas-Herald:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Chamidri Naotunna:** Writing – review & editing, Data curation. **Suet Ching Chen:** Writing – review & editing, Data curation. **Rosemarie Davidson:** Writing – review & editing, Data curation, Conceptualization. **Jairam Sastry:** Writing – review & editing, Data curation, Conceptualization. **Dermot Murphy:** Writing – review & editing, Data curation, Conceptualization. **M Guftar Shaikh:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization.

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.

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