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Investigating neuroblastoma in childhood opsoclonus-myoclonus syndrome

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ABSTRACT

Objective Opsoclonus-myoclonus syndrome (OMS) is a serious, often disabling neurological illness of early childhood which is frequently associated with occult neuroblastoma. As investigation methods vary significantly, the authors assessed the usefulness of imaging and metabolic studies in tumour detection.

Methods Retrospective case note review of 101 OMS patients from two paediatric neurology centres over 53 years.

Results The prevalence of neuroblastoma in OMS was 8% in the 1970s, 16% in the 1980s, 38% in the 1990s and 43% in the 2000s, with tumours being mainly low grade. CT/MR imaging of the chest and abdomen was the most accurate test to detect occult neuroblastoma. Poorer sensitivities were noted for metaiodobenzylguanidine scintigraphy and urine catecholamines, reflecting the low metabolic activity of these tumours.

Conclusion CT/MR imaging has the highest detection rate of neuroblastoma and this should be reflected in investigation protocols to achieve the best possible outcome for children with OMS.

What is already known on this topic

- Occult neuroblastoma is frequent in opsoclonus-myoclonus syndrome (OMS) and is most probably under-reported.
- Neuroblastoma in OMS tend to be low grade with better overall outcome.

What this study adds

- CT and MRI of the chest/abdomen are the most sensitive imaging modalities to detect occult neuroblastoma in OMS.
- Urinary catecholamines have poor diagnostic value in detecting occult neuroblastoma in OMS.

INTRODUCTION

Opsoclonus-myoclonus syndrome (OMS), also known as dancing eye syndrome, is a serious neurological illness with onset in early childhood; it is important to recognise this syndrome because of its common association with occult neuroblastoma.[1 2] The presenting symptoms of opsoclonus (rapid, multidirectional, conjugate eye movements), myoclonus, ataxia and behavioural change are often followed by a chronic relapsing disease course with persistent neurological and cognitive sequelae.[3–5] Affected individuals frequently become steroid dependent for years. Its pathogenesis is thought to be immune mediated, suggesting a cross-reactive autoimmunity between neuroblastoma cells and the central nervous system.[2] Up to one third of OMS cases have an atypical presentation and the time to diagnosis can frequently be delayed by weeks or months.[2 6] Neuroblastoma associated with OMS tends to be low grade with a more favourable outcome compared to non-OMS associated neuroblastoma. However, a significant mortality risk remains and detection of an underlying tumour can be vital.[1 7] Due to its small size and metabolically less active nature, investigation of an occult neuroblastoma can be challenging.[6 8] A recent population based study in the UK revealed that imaging practices vary considerably and frequently CT or MR imaging of the chest and abdomen was not performed, leading to a lower than expected occurrence of neuroblastoma cases.[6] The aim of this study was to determine the prevalence of OMS associated neuroblastoma in two large UK neurology centres and to systematically review the performed investigations and establish their sensitivity.

METHODS

We retrospectively reviewed the case records of 101 patients diagnosed with OMS over a period of 53 years at Great Ormond Street Hospital, London and the Royal Hospital for Sick Children, Glasgow. The follow-up data of this study will be published separately. For each patient the diagnosis was made by a paediatric neurologist based on clinical features and the investigations performed. We identified all those individuals with an underlying neural crest tumour and systematically documented the undertaking and outcome of the following investigations: chest x-ray, abdominal ultrasound scan, CT chest/abdomen, MR chest/abdomen, nuclear scintigraphy studies using radioiodinated metaiodobenzylguanidine (MIBG) and urine catecholamine metabolites (vanillylmandelic acid (VMA) and homovanillic acid (HVA)). Tumour location, staging and patient survival data were recorded. This study was approved by the research and development departments at Great Ormond Street Hospital in London and the Royal Hospital for Sick Children in Glasgow.

RESULTS

A neuroblastoma was identified in 21/101 cases and detection rates varied across decades, increasing through the study period (figure 1).

Tumour location was thoracic in seven (33%) and abdominal/pelvic in 14 (67%) cases. CT/MR imaging was performed in 15/21 patients (71%) and had a detection rate of 100%. MIBG was performed in 16/21 cases (76%) with a sensitivity of 75%. The detection rate of neuroblastoma via urine catecholamines was considerably lower at 24%. Table 1 summarises the investigation results.

Staging information revealed that 80% of tumours were low grade stage 1 and 2 neuroblastoma and 20% were stage 4 neuroblastoma. Twenty of 21 tumours were surgically resected. Two patients died as a consequence of relapsing neuroblastoma.

DISCUSSION

In this large review of investigations in OMS associated neuroblastoma, we estimate the neuroblastoma prevalence in OMS patients to be at least 43%, which agrees with the findings in a North American cohort.[2] The marked increase in detection rates over the last five decades is most likely attributable to the advances in imaging techniques. Recent results from immunological studies suggest that the rates of occult neuroblastoma might even be higher.[9] It has been shown that low grade tumours like those primarily found in OMS, tend to be smaller in size and are therefore more difficult to detect.[10] Our results confirm that primary investigations such as chest x-ray and abdominal ultrasound scans may be useful but lack sensitivity. Metabolic investigations such as the detection of urinary catecholamines were only helpful in 24% of cases, with rates being considerably lower than those expected in non-OMS associated neuroblastoma. This is almost certainly a reflection of the metabolically less active nature of tumours in our cohort. MIBG scintigraphy has become a standard and highly sensitive tool in the diagnosis and staging of neuroblastoma.[8] MIBG is a pharmacological analogue of norepinephrine and guanethidine and competes with biogenic amines for uptake and storage in adrenergic tissues. While overall false negative rates of MIBG scintigraphy tend to be around 8%, this percentage is considerably increased in children with stage 1 or 2 disease, where false negative rates can be as high as 24%. This is likely to be due to the non-secreting nature of low grade neuroblastoma.[8] Our results confirm that MIBG studies lack sensitivity, with figures ranging between 70% and 83%. CT/MR imaging of the chest and abdomen was the most accurate test in detecting occult neuroblastoma and was defined as the reference standard. If CT/MR imaging was performed after an alternative investigation was suggestive of the diagnosis of neuroblastoma, the CT/MR always identified the tumour. However, there were cases where CT/MR imaging identified a tumour that was not detected by other methods. Previous work has shown that CT and MR imaging are superior to ultrasound in detecting abdominal neuroblastoma; both CT and MR assessed tumour size and location equally well.[11] For thoracic tumours, MR imaging appears to be the single most useful test for detecting nodal, intraspinal and chest wall involvement.[12] Imaging of the neck, a common neuroblastoma site, is also recommended. For further staging purposes beyond initial tumour detection, a series of investigations are necessary to accurately determine the extent of disease, including a combination of MR, CT and MIBG scintigraphy.[13]

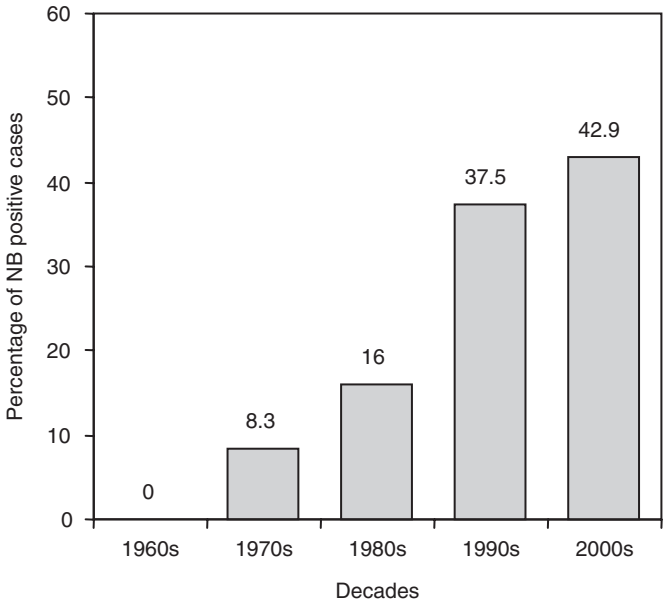

Figure 1 Neuroblastoma (NB) prevalence among patients with opsoclonus-myoclonus syndrome over the last five decades.

Limitations of this retrospective study are that patients have been investigated in various ways over the course of 53 years and we do not know how many neuroblastoma were missed overall. There has not been an accepted gold standard methodology for the investigation of OMS associated neuroblastoma.

A recent population based study of the presentation and management of OMS in the UK reported that only four out of 15 children (27%) had an underlying neuroblastoma detected.[6] Interestingly, none of these was identified via MIBG scans, chest x-ray or abdominal ultrasound imaging, but all were diagnosed via MR of the chest/abdomen. Among those individuals without apparent neuroblastoma, over a third had neither MR nor CT imaging performed, thus raising suspicion that an underlying neuroblastoma might have been missed. Despite the often benign nature and outcome of OMS associated neuroblastoma, mortality can still be significant as our

Table 1 Neuroblastoma investigation results in patients with OMS according to tumour location and imaging modality

Tumour location	Investigation	Positive result	Negative result	Not performed	Detection rate*
Thoracic (7 cases)	CXR	5	2	0	71%
	CT/MRI	5	0	2	100%
	MIBG	5	1	1	83%
Abdominal/pelvic (14 cases)	US abdomen	8	1	5	89%
	CT/MRI	10	0	4	100%
	MIBG	7	3	4	70%
Urine catecholamines		5	16	0	24%

*CT/MRI used as reference standard.
CXR, chest x-ray; MIBG, metaiodobenzylguanidine; OMS, opsoclonus-myoclonus syndrome; US, ultrasound.

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and previous reports demonstrate.[7] Even though our data suggest that the most sensitive individual tests to detect occult neuroblastoma are MR and CT imaging, the best investigation protocol may nevertheless include a combination of CT/MRI preceded by simple non-invasive tests such as chest x-ray and abdominal ultrasound scans. Urinary catecholamines and MIBG scans, on the other hand, might be useful to detect metabolically active tumours. This should be taken into account when devising investigation protocols for neuroblastoma detection and staging in children with OMS.

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Competing interests None.

Ethics approval This study was approved by the research and development departments at Great Ormond Street Hospital in London and the Royal Hospital for Sick Children in Glasgow (Reference: 08NS12).

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