Diagnosis and management of Sandifer syndrome in children with intractable neurological symptoms

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Abstract
Sandifer syndrome is a rare complication of gastro-oesophageal reflux disease (GERD) when a patient presents with extraoesophageal symptoms, typically neurological. The aim of this study was to review the existing literature and describe a typical presentation and most appropriate investigations and management for the Sandifer syndrome. A comprehensive literature search was performed via PubMed, Cochrane Library and NHS Evidence databases. Twenty-seven cases and observational studies were identified. The literature demonstrates that presenting symptoms of Sandifer’s may include any combination of abnormal movements and/or positioning of head, neck, trunk and upper limbs, seizure-like episodes, ocular symptoms, irritability, developmental and growth delay and iron-deficiency anaemia. A 24-h oesophageal pH monitoring was positive in all the cases of Sandifer’s where it was performed, while upper GI endoscopy ± biopsy and barium swallow were diagnostic only in a subset of cases. Successful treatment of the underlying gastro-oesophageal pathology led to a complete or near-complete resolution of the neurological symptoms in all of the cases.

Conclusion: It is evident from the literature that many patients with Sandifer syndrome were originally misdiagnosed with various neuropsychiatric diagnoses that led to unnecessary testing and ineffective medications with significant side effects. Earlier diagnosis of Sandifer’s would have allowed to avoid them.

What is Known:
• Sandifer syndrome is a rare complication of gastro-oesophageal reflux disease (GERD) when a patient presents with extraoesophageal symptoms, typically neurological.
• It may be difficult to recognise due to its non-specific presentation and lack of gastrointestinal symptoms.

What is New:
• Based on the review of 44 clinical cases of suspected Sandifer syndrome, the clinical picture was clarified: the presenting symptoms of Sandifer’s may include any combination of abnormal movements and/or positioning of head, neck, trunk and upper limbs, seizure-like episodes, ocular symptoms, irritability, developmental and growth delay and iron-deficiency anaemia.
• Successful treatment of the underlying gastro-oesophageal pathology led to a complete or near-complete resolution of the neurological symptoms in all of the reviewed cases.

Keywords Sandifer syndrome · Gastro-oesophageal reflux disease · Misdiagnosis · Intractable neurological symptoms

Abbreviations
EEG Electroencephalography
GERD Gastro-oesophageal reflux disease
GI Gastro-intestinal
MRI Magnetic resonance imaging

Introduction
Sandifer syndrome is defined as a rare complication of gastro-oesophageal reflux disease (GERD) when a patient presents with extraoesophageal symptoms, typically neurological [18]. These symptoms may be as severe as mimicking epileptic seizures or convulsions [23]. Although its pathophysiology is not completely understood, one possible explanation is that
neurological manifestations are the consequence of vagal re-
flex with the reflex center in nucleus tractus solitarii [3]. The
main difficulty with accurately diagnosing this clinical presen-
tation is that often the overt gastro-intestinal symptoms, such
as abdominal pain, vomiting or indigestion, are either absent,
or the patient is too young to be able to communicate them.
Thus, there is nothing to point the clinician to the direction of
GI investigations, and as a result, the vast majority of patients
with Sandifer syndrome are originally misdiagnosed with a
neurological or a musculoskeletal disorder. This may lead to
a range of unnecessary investigations, such as EEG, MRI and
electromyographic studies, all of which come back normal.
Moreover, this may result in the administration of unnecessary
medications, such as anti-epileptic agents, which may have
significant negative side effects. The aim of this study is to
review the existing literature and describe a typical presenta-
tion and most appropriate investigations and management for
the Sandifer syndrome, so that it can be considered early on in
the differential diagnosis for children with intractable neuro-
logical symptoms.

Methodology

The literature search strategy included conducting a systemat-
ic review via Cochrane Library, PubMed and NHS Evidence
databases. The search terms and the outcomes are listed
below:

- Cochrane library: ‘Sandifer* syndrome’
  - 1 controlled trial, not relevant
- PubMed search: ‘Sandifer* syndrome’
  - 86 results in the English language, 27 were relevant
  - The following publications were excluded:
    - Case studies covering only adults
    - Correspondence that did not include specific patient cases
- NHS Evidence: ‘Sandifer* syndrome’
  - 8 results, 1 was relevant (NICE guideline)

Overall, 27 case reports and observational studies were
available for analysis, covering 44 clinical cases in total.

Results

The detailed findings of the systematic review are pro-
vided in Table 1.

The literature demonstrates that the presenting symptoms
of Sandifer syndrome may include any combination of abnor-
mal movements and/or positioning of head, neck, trunk and
upper limbs, seizure-like episodes, ocular symptoms, irritabil-
ity, developmental and growth delay and iron-deficiency anae-
mia. It is evident from the literature that many of the patients
were originally misdiagnosed with various neuropsychiatric
diagnoses that led to unnecessary testing and ineffective medi-
cations that may have caused significant side effects. Earlier
diagnosis of Sandifer’s would have allowed to avoid them.

As Sandifer syndrome is caused by gastro-oesophageal reflux,
its investigations and management should be consistent with
those of GERD. In terms of diagnostic procedures, 24-h oesoph-
ageal pH monitoring was positive in all the cases of Sandifer’s
where it was performed, while upper GI endoscopy ± biopsy and
barium swallow were diagnostic only in a subset of cases.

A range of treatment options were applied in the reviewed
literature, including dietary changes (cow’s milk exclusion,
amino-acid-based formula), pharmacological management
(alginates, proton pump inhibitors (PPIs)), enteral tube feed-
ing, and surgical approach, when conservative management
was ineffective (Nissen fundoplication is usually curative).
The pharmacological treatment was often sufficient on its
own to achieve the resolution of symptoms; however, further
escalation of management was required in the cases of ad-
vanced disease. These treatment options are consistent with
the 2015 NICE guideline on management of GERD in chil-
dren and young people [22].

Successful treatment of the underlying gastro-oesophageal
pathology led to a complete or near-complete resolution of the
neurological symptoms in all of the reviewed cases.

Discussion

1. Sandifer syndrome may be difficult to recognise due to its non-
specific presentation; however, it is an important differential
diagnosis to consider in children with neurological symptoms
that remain unexplained by neurological investigations.
2. When Sandifer syndrome is suspected, 24-h oesophageal pH
monitoring is usually diagnostic; however, an empirical trial
of pharmacological management (e.g., prescribing a PPI) is
also appropriate without prior invasive investigation [31].
3. Once diagnosed, it can be successfully managed by treating
the underlying GERD/hiatus hernia which typically leads to
a complete resolution of all associated symptoms.
4. In the majority of patients, pharmacological management
is sufficient for the resolution of symptoms. Other treat-
ment options include dietary modifications, enteral tube
feeding, and surgical management.
5. The choice of a management plan in each case depends on
the severity and duration of the underlying condition, as
well as individual responsiveness to treatment.
| Ref. no. | Reference                        | Study group size | Key results                                                                 | Diagnostic investigation                              | Definitive treatment | Outcome: complete resolution of symptoms? | Comments: prior misdiagnosis (e.g. neurological)? |
|---------|----------------------------------|------------------|-----------------------------------------------------------------------------|------------------------------------------------------|----------------------|------------------------------------------|-------------------------------------------------|
| [1]     | Bamji et al. (2015)              | 2                | Abnormal body posturing, irritability                                        | None, empirical treatment                            | Dietary              | Yes                                      |                                                 |
| [20]    | Nalbantoglu et al. (2013)        | 1                | Abnormal posturing and movement of head and neck; ocular deviation           | Oesophageal pH monitoring, oesophageal biopsy         | Dietary              | Yes                                      |                                                 |
| [30]    | Tokuhara et al. (2008)           | 1                | Growth retardation, abnormal neck movement, anaemia, hypoproteinaemia        | Upper GI endoscopy with biopsy; 24-h pH monitoring   | Surgical             | Yes                                      |                                                 |
| [15]    | Kostakis et al. (2008)           | 1                | Abnormal head posturing                                                      | n/a                                                | n/a                  | n/a                                      |                                                 |
| [16]    | Lehwald et al. (2007)            | 1                | Abnormal posturing and movement of head and neck                             | Upper GI endoscopy                                   | Surgical             | Near complete                            | Yes                                             |
| [9]     | Firat et al. (2007)              | 1                | Abnormal movements of head and neck, motor and speech delay                  | Oesophageal pH monitoring, upper GI fluoroscopy       | Surgical             | Yes                                      | Yes                                             |
| [13]    | Kabakus, Kurt (2006)             | 4                | Abnormal posturing and movements of head and neck, ocular                    | Gastro-oesophageal scintigraphy                      | Dietary and lifestyle, pharmacological              | Near complete                            | Yes                                             |
| Ref. no. | Reference                     | Study group size | Key results                                                                 | Diagnostic investigation | Definitive treatment | Outcome: complete resolution of symptoms? | Comments: prior misdiagnosis (e.g. neurological)? |
|---------|-------------------------------|------------------|-----------------------------------------------------------------------------|--------------------------|----------------------|------------------------------------------|-----------------------------------------------|
| [5]     | Corrado et al. (2006)         | 1                | Abnormal posturing and movement of head, neck and trunk                     | 24-h gastro-oesophageal pH monitoring | Yes                  |                                          |                                               |
|         |                               |                  | deviation, irritability, growth retardation, anaemia                       |                          |                      |                                          |                                               |
| [10]    | Frankel et al. (2006)         | 1                | Abnormal head posturing, irritability                                       | Oesophageal pHmetry, surface electromyography, split-screen videography | Surgical             | Yes                                      | Yes                                           |
|         |                               |                  |                                                                             |                          |                      |                                          |                                               |
| [7]     | Demir et al. (2001)           | 1                | Abnormal positioning and movements of neck, hand tremor, vomiting, stridor  | Barium oesophagogram    | Pharmacological      |                                          | n/a                                          |
| [6]     | de Ybarrondo, Mazur (2000)    | 1                | Cerebral palsy, severe developmental delay, asthma                         | n/a                     | n/a                  |                                          |                                               |
| [4]     | Corrado et al. (2000)         | 1                | Abnormal movements of head, neck, trunk                                    | 24-h pH oesophageal monitoring | Dietary             | Yes                                      |                                               |
| [29]    | Tekou et al. (1997)           | 1                | Abnormal posturing of                                                       | n/a                     | Surgical             | Yes                                      |                                               |
| Ref. no. | Reference                  | Study group size | Key results                                                                 | Diagnostic investigation                                      | Definitive treatment | Outcome: complete resolution of symptoms? | Comments: prior misdiagnosis (e.g. neurological)? |
|---------|----------------------------|------------------|-------------------------------------------------------------------------------|--------------------------------------------------------------|----------------------|------------------------------------------|-------------------------------------------------|
| [2]     | Cardi et al. (1996)        | 1 n/a            | Head and neck posturing, irritability, cough, hoarseness                      | Real-time ultrasonography                                    | n/a                  | n/a                                      | Had no previous diagnosis.                      |
| [8]     | Deskin (1995)              | 1                | Abnormal neck posturing, irritability, cough, hoarseness                      | Barium swallow                                                | Surgical             | Yes                                      |                                                |
| [11]    | Gorrotxategi et al. (1995) | 8                | Abnormal neck posturing                                                      | Barium swallow, 24-h pH-monitoring, manometry, endoscopy, biopsy | Surgical (3 patients), pharmacological (5 patients) | Significant improvement |                                                |
| [26]    | Senocak et al. (1993)      | 1                | Abnormal neck posturing                                                      | n/a                                                          | Surgical             | Yes                                      |                                                |
| [28]    | Sommer (1993)              | 13               | Developmental delay, abnormal behaviour, hoarse growling cry (all patients had Brachmann-n-de Lange syndrome) | 3 patients—barium swallow, 10 patients—pH probe monitoring of upper GI system, esophagoscopy, endoscopy | Pharmacological and dietary (5 patients), surgical (8 patients) | Significant improvement |                                                |
| [25]    | Puntis et al. (1989)       | 1                | Abnormal posturing and movements of head,                                    | Barium swallow, oesophageal pH monitoring.                    | Surgical             | Yes                                      |                                                |
| Ref. no. | Reference                    | Study group size | Key results                                                                                                                                   | Diagnostic investigation | Definitive treatment | Outcome: complete resolution of symptoms? | Comments: prior misdiagnosis (e.g. neurological) |
|---------|------------------------------|------------------|---------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|----------------------|------------------------------------------|-----------------------------------------------|
|         |                              |                  | Extraoesophageal symptoms                                                                                                                  |                          |                      |                                          |                                               |
|         |                              |                  | neck, trunk, anaemia                                                                                                                        | upper GI endoscopy and biopsy |                      | Yes                                      | Yes                                           |
| [17]    | Mandel et al. (1989)         | 3                | Abnormal posturing and movements of head and trunk, weight loss                                                                          | 12-h lower oesophageal pH monitoring |                      | Yes                                      |                                               |
|         |                              |                  |                                                                                                                                             |                          | Pharmacological      | Yes                                      |                                               |
| [21]    | Nanayakkara, Paton (1985)    | 3                | Abnormal posturing and movements of head, neck and trunk                                                                                 | Barium study             | Pharmacological       | Yes                                      |                                               |
|         |                              |                  |                                                                                                                                             |                          | dietary              | Yes                                      |                                               |
| [12]    | Hadari et al. (1984)         | 1                | Abnormal posturing and movements of body and limbs, seizure-like episodes, hypotonia, developmental delay                                 | Barium study             | Pharmacological       | Yes                                      |                                               |
|         |                              |                  |                                                                                                                                             |                          |                      | Yes                                      |                                               |
| [21]    | Nanayakkara, Paton (1985)    | 3                | Abnormal movements of neck and trunk, irritability                                                                                          | n/a                       | Pharmacological       | Yes                                      |                                               |
| [12]    | Hadari et al. (1984)         | 1                | Abnormal posturing and movements of head and neck                                                                                            | n/a                       | Surgical             | Yes                                      |                                               |
| Ref. no. | Reference                        | Study group size | Key results                                                                 | Diagnostic investigation | Definitive treatment | Outcome: complete resolution of symptoms? | Comments: prior misdiagnosis (e.g., neurological)? |
|----------|---------------------------------|------------------|-----------------------------------------------------------------------------|--------------------------|---------------------|------------------------------------------|--------------------------------------------------|
| [14]     | Keren et al. (1983)             | 1                | Abnormal posturing and movement of head and trunk                          | Barium study             | n/a                 | n/a                                      |                                                   |
| [27]     | Smallpiece, Deverall (1982)     | 1                | Irritability, abnormal posturing and movements of head, neck, trunk, growth delay | Barium swallow           | Surgical            | Yes                                      |                                                   |
| [32]     | Werlin et al. (1980)            | 5                | Abnormal body posturing                                                    | n/a                      | n/a                 | n/a                                      |                                                   |
| [19]     | Murphy, Gellis (1977)           | 2                | Abnormal neck posturing                                                    | XR studies               | Pharmacological     | Yes                                      |                                                   |
| [24]     | O’Donnell, Howard (1971)        | 1                | Abnormal head and neck posturing, strabismus, anaemia                      | n/a                      | n/a                 | n/a                                      | Yes                                              |

1 Information not available
Compliance with ethical standards

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

Ethical approval  This article does not contain any studies with human participants or animals performed by any of the authors.

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