

Butterfly Vertebrae: A Systematic Review of the Literature and Analysis

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Abstract

Study Design: Systematic review (Level 4)

Objective: To summarize the demographics, clinical presentations, and conditions associated with butterfly vertebrae.

Methods: A systematic search was performed of multiple databases. A total of 279 articles were identified for screening. Case series or case reports of butterfly vertebrae with adequate clinical detail were compiled.

Results: Eighty-two total articles (109 patients) were selected for final inclusion. Sixty-one percent of patients presented with a single butterfly vertebra, while 39% were multiple. The most common location for butterfly vertebrae was T1. Fifty-six percent of cases were associated with a syndrome, the most common being spondylocostal dysostosis. The presence of multiple butterfly vertebra was strongly associated with a syndrome or additional anomalies ($P < .001$). Overall, the most common presenting complaint was low back pain. Seventy percent of patients had associated spinal disease. Other organ systems affected included musculoskeletal (43%), craniofacial (30%), neurologic (27%), cardiovascular (24%), genitourinary (23%), gastrointestinal (22%), laboratory abnormality (16%), and endocrine (9%).

Conclusions: This study is the largest collection of butterfly vertebrae cases to date. Butterfly vertebrae are associated with spinal deformity and multiple butterfly vertebrae may indicate a syndromic illness. Low back pain or disc herniation may occur with lumbar butterfly vertebrae however the etiology of this phenomena has not been rigorously explained. Many diseases and syndromes are associated with butterfly vertebrae.

Keywords

butterfly vertebrae, anterior rachischisis, sagittal cleft vertebrae, congenital spine, spinal malformation, Klippel-Feil syndrome, Alagille syndrome, spondylocostal dysostosis

Introduction

A butterfly vertebra (sagittal cleft vertebra or anterior rachischisis) is a sagittal defect in the vertebral body caused by failure of fusion of the 2 lateral chondrification centers during embryogenesis.^{1,2} The name is based on the appearance of the 2 hemivertebrae emerging as butterfly wings from the central cleft on x-ray.³ This malformation has been reported to be exceptionally rare in the literature.^{1,3-9}

Several sources cite the association between butterfly vertebrae and congenital diseases such as Alagille syndrome, Jarcho-Levin syndrome, Crouzon syndrome, and Pfeiffer's syndrome.^{9,10} Reports have also associated butterfly vertebrae with low back pain.^{1,7,9,11} Because of their rarity, they can easily be misclassified as other pathologic processes.^{12,13} The true incidence, as well as the full spectrum of related conditions, are unknown as many are only picked up incidentally.

The largest previous series of butterfly vertebrae was published by Cave³ in 1957, in which he reviewed 33 cases in the literature. However, detailed clinical data from these cases was not reported.³ Later, Kapetanakis et al¹¹ reviewed the literature and reported on 11 cases published between 1990 and 2015. To our knowledge, a comprehensive analysis of all butterfly

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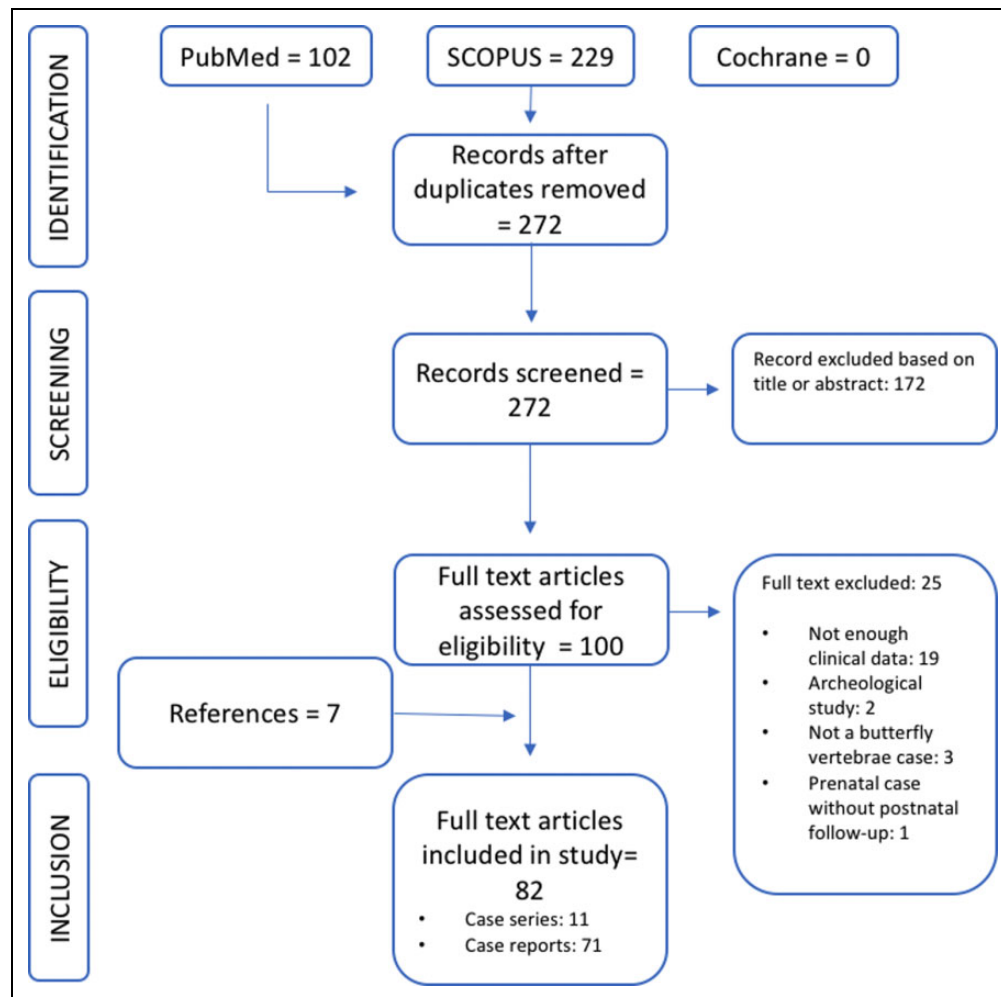


Figure 1. Study selection based on PRISMA (Preferred Reporting for Systematic Reviews and Meta-Analyses) guidelines.

vertebrae cases has not been performed. The goal of this study was to assimilate all reports of butterfly vertebrae in the literature to formulate a review and glean new information about this rare malformation. We were specifically interested in the rate of associated abnormalities in other organ systems occurring through concurrent syndromes. Furthermore, we wished to determine the implications, if any, of discovering incidental butterfly vertebrae with regard to clinical workup.

Materials and Methods

A systematic review was prepared according to the protocol set forth by the Cochrane Collaboration and Wright et al and reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Figure 1).¹⁴⁻¹⁶ In November 2017, an electronic search was performed on the Scopus and PubMed databases, as well as the Cochrane Library, to identify studies containing the following terms: “butterfly vertebrae,” or its common synonyms “sagittal cleft vertebrae” and “anterior rachischisis.” Two independent reviewers screened titles and abstracts from

which full-length texts were selected. References contained in the selected texts were also reviewed for possible sources. Furthermore, major journals were hand-searched for recent publications that might not have been included in the initial search.

Studies that contained individual or case series of patients having single or multiple butterfly vertebrae, either in isolation or part of a constellation of anomalies, were included if they contained the following clinical details: age (at final exam or follow up), sex, location, and number of butterfly vertebrae. Several studies with relevant clinical data that were missing a single part of the above information were included in our analysis only for those data sets to which they were applicable.

Articles were excluded if they did not involve butterfly vertebrae, did not present discrete cases of butterfly vertebrae, pertained primarily to archeological studies or veterinary studies, involved prenatal patients without postnatal follow up, were in languages not translatable by the researchers, or the article could not be located despite exhaustive archive review (typically due to age of the article). Studies were also excluded

Table 1. List of Included Cases.

Author	Year	Age (Years)	Sex	Single or Multiple	Location	Syndrome	Spine	GU	Cardiac	GI	Endo	Neuro	Lab	MSK	CF
Frederick	1945	38	M	Single	L3	None	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Frederick	1945	23	M	Single	T7	None	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Franciosi	1951	28	M	Multiple	L3, L4	None	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Cave	1957	32	F	Single	T7	None	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Lagarde	1960	20	F	Multiple	L3, L4	None	(+)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Lagarde	1960	26	F	Single	T12	None	(+)	(-)	(+)	(-)	(-)	(-)	(-)	(-)	(-)
Schwartz	1960	28	M	Single	T7	Calyceal diverticuli	(-)	(+)	(+)	(-)	(-)	(-)	(+)	(+)	(-)
Schwartz	1960	18	M	Single	T11	Calyceal diverticuli	(-)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Colquhoun	1968	12	F	Single	T9	None	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Colquhoun	1968	46	M	Single	T7	None	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Colquhoun	1968	56	F	Single	T11	None	(+)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Colquhoun	1968	46	F	Single	T11	None	(+)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Tamagawa	1972	25	F	Single	T7	None	(+)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Mitchell	1981	0.42	F	Multiple	T8	4q21 Interstitial deletion	(+)	(-)	(+)	(+)	(-)	(+)	(+)	(+)	(+)
De Graaf	1982	39	M	Single	L5	None	(+)	(-)	(-)	(-)	(-)	(+)	(-)	(-)	(-)
Dastur	1985	13	M	Single	L2	Goldenhar	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(+)
Garcia-Cruz	1985	16	M	Multiple	T2-T9	20p12.2 deletion	(+)	(-)	(+)	(-)	(+)	(+)	(-)	(+)	(+)
Schlitt	1989	42	F	Single	C4	Klippel-Feil	(+)	(-)	(+)	(-)	(+)	(+)	(+)	(-)	(-)
Rose	1991	0.13	M	Multiple	T4, T6	Deletion of 4(q21q25)	(+)	(+)	(+)	(-)	(-)	(+)	(+)	(+)	(+)
Mahajan	1992	24	F	Single	T11	Mullerian agenesis	(+)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Garcia	1993	58	F	Single	T11	None	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Garcia	1993	61	F	Single	T11	None	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
McCall	1994	7.67	M	Multiple	Not reported	Jarcho-Levin, spondylocostal dysostosis	(+)	(-)	(+)	(+)	(-)	(-)	(-)	(+)	(+)
Maillefert	1995	34	M	Multiple	T8, T10	Alagille	(-)	(-)	(-)	(+)	(-)	(-)	(+)	(-)	(+)
Delgado	1996	41	M	Single	L3	None	(+)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Herman	1996	0.06	F	Single	T7	I-cell disease (neonatal type II mucopolidosis)	(-)	(-)	(-)	(-)	(+)	(-)	(+)	(+)	(-)
Funke	2001	31	M	Single	T8	None	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Sonel	2001	37	M	Single	L3	None	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Brasili	2002	36	F	Multiple	L5, S1	None	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Przkora	2002	14	F	Multiple	T1, T4, T7, T8, T10, T11, L3	Alagille	(+)	(-)	(+)	(+)	(+)	(-)	(-)	(+)	(-)
Chan	2003	1.15	M	Multiple	T1-T5	Klippel-Feil	(+)	(+)	(-)	(-)	(-)	(+)	(-)	(+)	(-)
Ryan	2003	39	F	Multiple	T6, T8	Alagille	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(-)
Anderson	2003	7	N/A	Single	C3	Pfeiffer's	(+)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Rahimi-Movaghgar	2004	15	M	Multiple	T2-T6	Klippel-Feil	(+)	(-)	(-)	(-)	(-)	(+)	(-)	(+)	(+)
Sarpathy	2004	13	F	Single	L1	None	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Dejardin	2004	6	F	Single	Lumbar, not specified	None	(-)	(+)	(+)	(-)	(-)	(+)	(-)	(-)	(+)
Anderson	2005	0.17	M	Single	C6	Goldenhar	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(+)
Anderson	2005	8	M	Single	T4	Goldenhar	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(+)

(continued)

Table 1. (continued)

Author	Year	Age (Years)	Sex	Single or Multiple	Location	Syndrome	Spine	GU	Cardiac	GI	Endo	Neuro	Lab	MSK	CF
Anderson	2005	1	M	Single	C4	Goldenhar	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(+)
Vázquez-López	2005	0.65	F	Multiple	T3-T5, L3	Jarcho-Levin, spondylocostal dysostosis	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(-)
Ahn	2005	12	F	Multiple	Multiple, thoracic not specified	Delta phalanges plus	(+)	(-)	(+)	(-)	(-)	(+)	(-)	(+)	(+)
Atar	2006	2	M	Single	T9	Kabuki	(+)	(-)	(-)	(-)	(-)	(+)	(-)	(-)	(+)
Takikawa	2006	4	M	Multiple	C6, C7	Spondylocostal dysostosis	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(-)
Takikawa	2006	2	F	Multiple	C6, C7	Spondylocostal dysostosis	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(-)
Takikawa	2006	4	F	Multiple	L5, S1	Spondylocostal dysostosis	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(-)
Takikawa	2006	3	M	Multiple	L5, S1-S3	Spondylocostal dysostosis	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(-)
Takikawa	2006	5.5	M	Multiple	C6, C7, T1-T3, L4, L5, S1, S2	Spondylocostal dysostosis	(+)	(-)	(-)	(+)	(-)	(-)	(-)	(+)	(-)
Takikawa	2006	0.17	F	Single	T11	Spondylocostal dysostosis	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(+)
Takikawa	2006	6.5	F	Multiple	C6, C7	Spondylocostal dysostosis	(+)	(-)	(+)	(-)	(-)	(-)	(-)	(+)	(-)
Takikawa	2006	18	F	Multiple	C6, C7	Spondylocostal dysostosis	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(+)
Takikawa	2006	18	F	Multiple	C5, C7	Spondylocostal dysostosis	(+)	(+)	(-)	(-)	(-)	(+)	(-)	(+)	(-)
Takikawa	2006	17	F	Multiple	C5, C7, T4	Spondylocostal dysostosis	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(-)
Takikawa	2006	13	F	Multiple	T6-T8	Spondylocostal dysostosis	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(-)
Takikawa	2006	0.75	M	Multiple	C6, C7, L2, S1, S2	Spondylocostal dysostosis	(+)	(-)	(-)	(+)	(-)	(-)	(-)	(+)	(-)
Takikawa	2006	5	M	Multiple	C5, C6, L2 C7, S1, S2	Spondylocostal dysostosis	(+)	(+)	(-)	(+)	(-)	(-)	(-)	(+)	(-)
Takikawa	2006	3	M	Multiple	C6, C7	Spondylocostal dysostosis	(+)	(+)	(+)	(+)	(-)	(-)	(-)	(+)	(-)
Takikawa	2006	2	M	Multiple	T6, T9, T10, T12	Spondylocostal dysostosis	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(-)
Takikawa	2006	9.5	M	Multiple	T4, T5	Spondylocostal dysostosis	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(-)
Takikawa	2006	2	F	Multiple	T7, T9	Spondylocostal dysostosis	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(-)
Zeglam	2006	2.5	F	Single	T12	None	(+)	(-)	(-)	(-)	(-)	(+)	(-)	(+)	(-)
Zeglam	2006	54	M	Single	L4	None	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Pasku	2007	25	F	Single	C2	None	(+)	(-)	(-)	(-)	(-)	(+)	(-)	(-)	(-)
Rossi	2007	7	F	Single	T8	Lathosterolosis	(-)	(+)	(-)	(-)	(-)	(+)	(+)	(+)	(+)
Robert	2007	5	M	Multiple	Nonspecific thoracic and lumbar	Alagille	(-)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)
Küpel	2008	0.17	F	Multiple	T3, T8	Wilms' tumor	(+)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Patinharayil	2008	46	F	Single	T6	None	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Wang	2008	2	N/A	Single	T6	Alagille	(-)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)
Wang	2008	5	N/A	Multiple	T3, T4	Alagille	(-)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)
Wang	2008	3	N/A	Multiple	T4, T6-T10	Alagille	(-)	(-)	(+)	(+)	(+)	(-)	(+)	(-)	(+)
Wang	2008	4	N/A	Multiple	T4, T7, T9	Alagille	(-)	(-)	(-)	(+)	(+)	(-)	(+)	(-)	(+)
Wang	2008	2	N/A	Multiple	T4-T9	Alagille	(-)	(+)	(-)	(-)	(-)	(-)	(+)	(-)	(+)
Ekim	2010	32	M	Single	L2	None	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Qian	2010	26	M	Single	L4	Ankylosing spondylitis	(+)	(-)	(-)	(-)	(-)	(-)	(+)	(-)	(-)
Qian	2010	40	M	Single	L5	Ankylosing spondylitis	(+)	(-)	(-)	(-)	(-)	(-)	(+)	(-)	(-)
Tuncel	2010	27	M	Single	L2	None	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Boulet	2011	35	M	Single	S1	None	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(-)
Cho	2011	56	F	Single	L4	None	(+)	(-)	(-)	(-)	(-)	(+)	(-)	(-)	(-)

(continued)

Table 1. (continued)

Author	Year	Age (Years)	Sex	Single or Multiple	Location	Syndrome	Spine	GU	Cardiac	GI	Endo	Neuro	Lab	MSK	CF
Choi	2011	46	M	Single	C1	None	(+)	(-)	(-)	(-)	(-)	(+)	(-)	(-)	(-)
Choi	2011	5	M	Single	C4	None	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Cui	2011	13	F	Single	L6	None	(+)	(-)	(-)	(-)	(-)	(+)	(-)	(-)	(-)
Massobrio	2011	5	M	Multiple	T7-T11	Alagille	(-)	(-)	(-)	(+)	(-)	(-)	(-)	(+)	(+)
Jarzabek	2012	24	F	Multiple	T9-T11	Kallman	(+)	(-)	(-)	(-)	(+)	(+)	(-)	(+)	(+)
Jarzabek	2012	28	M	Single	L2	Kallman	(+)	(+)	(-)	(-)	(-)	(+)	(-)	(-)	(+)
Kilgore	2012	33	M	Single	T8	None	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Zarate	2012	0.75	F	N/A	N/A	Kabuki	(-)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)
Ditkofsky	2013	51	F	Single	T9	None	(+)	(-)	(-)	(+)	(+)	(+)	(-)	(+)	(+)
Zuo	2013	24	F	Single	L4	None	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Patra	2013	10	F	Single	C2	None	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Aygun	2014	0.06	M	Single	T8	None	(-)	(+)	(+)	(+)	(-)	(-)	(-)	(+)	(+)
Canitez	2014	0.33	F	Single	T7	Lung agenesis	(-)	(+)	(+)	(-)	(-)	(-)	(-)	(+)	(+)
Ekiz	2014	40	M	Single	L4	None	(+)	(-)	(-)	(-)	(-)	(+)	(-)	(-)	(-)
Frost	2014	54	M	Single	T8	None	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Sandal	2014	0.67	M	Multiple	T9, T11	VACTERL	(-)	(+)	(+)	(+)	(-)	(-)	(-)	(+)	(-)
Youssef	2014	0.5	M	Single	T12	None	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Cheng	2015	50	F	Multiple	T10, L2, L4	None	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Diehl	2015	3	F	Multiple	T5, T7	Micro duplication of 22q11.21	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Hawkes	2015	1	F	Multiple	T9, T10	Myhre	(+)	(-)	(-)	(-)	(-)	(+)	(-)	(+)	(+)
Hopkins	2015	21	M	Single	L4	None	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Karagyris	2015	40	F	Single	L4	None	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Ozaras	2015	38	M	Multiple	T9, L3	Behçet's disease	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Sifuentes	2015	62	F	Single	T10	None	(+)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Esen	2016	5.5	F	Single	T12	None	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Esen	2016	56	M	Single	L4	None	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Guo	2016	4	M	Single	T1	None	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Kapetanakis	2016	40	F	Single	S1	None	(+)	(-)	(-)	(-)	(-)	(+)	(-)	(-)	(-)
Karaca	2016	42	F	Single	T1	Klippel-Feil	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Slouma	2016	55	F	Multiple	T9-T12, L3	None	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Deepak	2017	14	M	Single	C3	None	(+)	(-)	(-)	(+)	(-)	(-)	(-)	(-)	(-)
Hannoush	2017	1	M	Multiple	T4, T6, T8	Alagille	(-)	(+)	(+)	(+)	(-)	(-)	(+)	(-)	(+)

Abbreviations: M, male; F, female; GU, genitourinary; Cardiac, cardiovascular/chest; GI, gastrointestinal; Endo, endocrine; Neuro, neurologic; Lab, laboratory values; MSK, musculoskeletal/other; CF, craniofacial; N/A, not available; VACTERL, vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities.

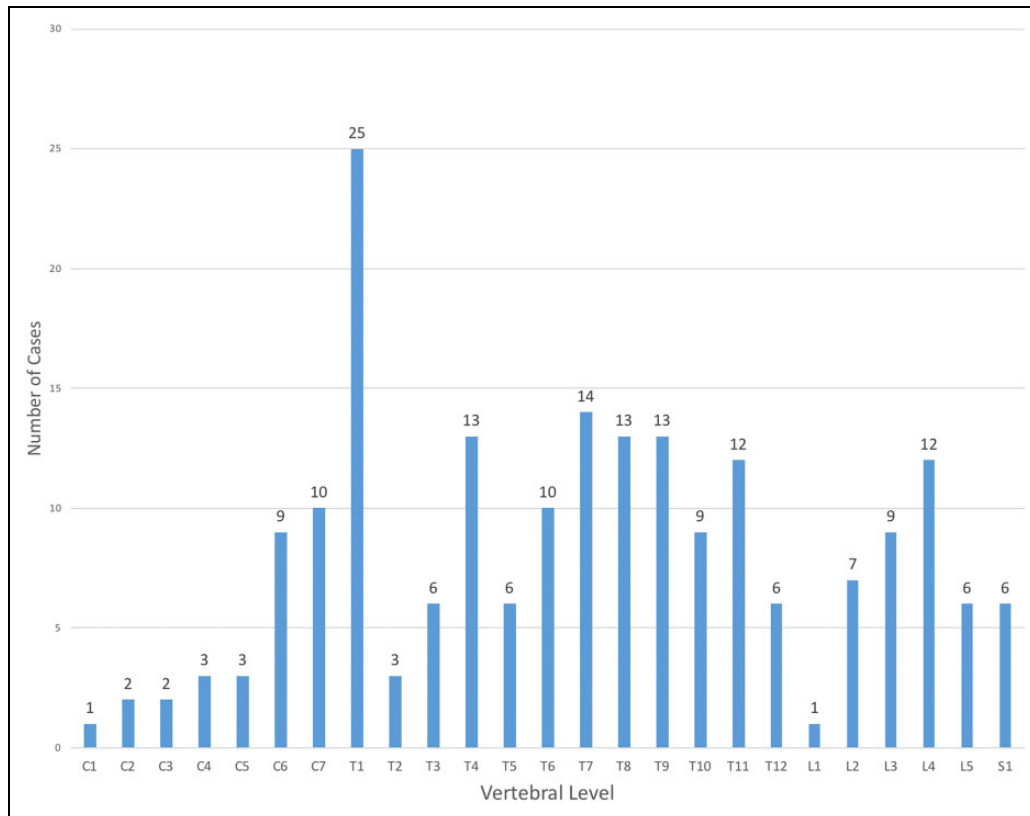


Figure 2. Prevalence of butterfly vertebrae at vertebral levels.

if they lacked sufficient clinical data to be included for analysis (greater than 2 of the above inclusion points).

Following the selection of articles, clinical cases were aggregated for analysis,¹⁷ and the following variables were considered for extraction: age, sex, location of butterfly vertebrae in the spine, number of butterfly vertebrae, presenting complaint, concomitant syndrome or systemic illness, other spinal abnormality excluding butterfly vertebrae, abnormal laboratory findings, and finally abnormalities of the genitourinary, cardiac, endocrine, neurologic, craniofacial, or musculoskeletal systems. Systems abnormalities were collected and sorted into these groups based on the valid positive associated findings as reported by the authors of the case. A patient was considered to have “a normal system” if it was not specifically identified in the article. For simplicity, we use the term “syndrome” to indicate any syndrome, sequence, association, or other condition affecting multiple organ systems.

Article quality was appraised based on complete review of the imaging and clinical information presented in the text. A bias review was deemed unnecessary as these studies were case reports and case series.

Statistics

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software (version 24.0, IBM Corp, Armonk, NY, USA). The chi-square test was used to test the association between multiple versus single butterfly

vertebrae and the presence or absence of a syndrome or other systemic illness.

Results

The Scopus search yielded 229 citations while PubMed yielded 102, for a total of 331 articles. A search of the Cochrane library yielded 0 results. After duplicates were removed there were 272 citations in total. From these 172 citations were excluded based on analysis of the abstract or title for the following reasons: was not a case of butterfly vertebrae (125 citations), the article was not available (15 citations), was a prenatal article (14 citations), was an archeological study (10 citations), was a veterinary study (7 articles), or could not be translated (1 citation). 100 articles were included for full review from this group with an additional 7 added based on review of references (107 articles). From this group, another 25 articles were excluded for the following reasons: not enough clinical data (19 articles), was not a case of butterfly vertebrae (3 articles), was an archeological study (2 articles), was a prenatal case without postnatal follow-up (1 article). After careful review of abstracts and full articles, a total of 82 articles (109 cases of butterfly vertebrae) were included for final review (Figure 1). Of the 109 cases included, 11 were categorized as lacking a single data point, and thus grouped separately (5 cases lacked specific vertebral location of the butterfly vertebrae, 6 lacked the sex of the patient) (Table 1). Therefore, these cases were not included

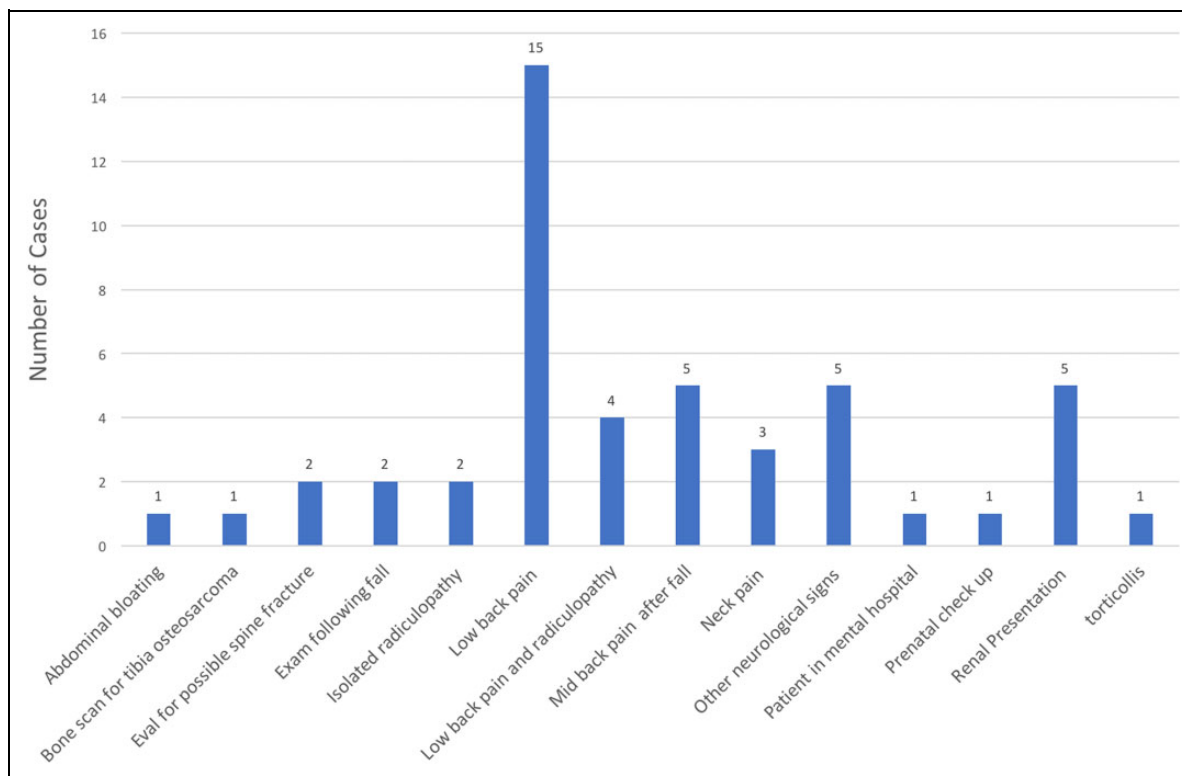


Figure 3. Most common presenting complaints in nonsyndromic cases.

in the calculation of average sex and location of butterfly vertebrae.

Clinical Characteristics

The average age of patients in this group was 20.5 years. Fifty-one of 103 cases were female (50%). Sixty-three cases were single vertebrae (61%), while 41 of 104 cases were multiple (39%). The most common location was T1 (25 cases), followed by T7 (14 cases) (Figure 2).

The most common presenting complaint was low back pain (23%, 25/109 cases), followed by neck pain (0.05%, 5/109) and jaundice (0.05%, 5/109). When examining only nonsyndromic cases, low back pain was still the most common presenting complaint (30%, 14/48 patients), followed by mid back pain (10%, 5/48 patients). Of note 5/48 cases (10%) were reports of butterfly vertebrae being mistaken for either fracture or tumor. See Figure 3 for most common presenting complaints.

Of the 109 cases, 48 patients did not have an associated syndrome (44%), while 61 patients did have an associated syndrome (56%). The most common of these syndromes was spondylocostal dysostosis with 17 cases (28%) followed by Alagille syndrome with 11 cases (18%) (Figure 4). The presence of multiple butterfly vertebrae (>1) was associated with the presence of a syndrome (40/45 cases, 90%), while single butterfly vertebrae were more likely to occur alone (43/64 cases, 67%): $\chi^2(1, n = 108) = 34.7, P < .001, \phi$ coefficient = -0.57 (Figure 5).

Associated Conditions

The most common associated organ system affected was “Other spinal deformity or disease,” which included any structural abnormality of the spine outside the butterfly vertebrae. There were 76 of 109 patients affected in this category (70%) with scoliosis as the most common finding. Other findings included failure of formation and segmentation, block vertebrae, kyphosis, spina bifida, disc herniation, spondylolisthesis, vertebral body abnormality, syringomyelia, and myelomeningocele. There was no significant association between “other spinal deformity” and the presence of single or multiple butterfly vertebrae: $\chi^2(1, n = 108) = 0.11, P = .96, \phi = -0.01$.

The next most common associated organ system affected was “Other skeletal deformity or disease” with 46 of 109 patients affected (43%). The most common finding was rib fusion or abnormality. Other abnormalities included short stature, clinodactyly, syndactyly, polydactyly, brachydactyly, thumb hypoplasia, short dysplastic femurs, and radioulnar synostosis.

Craniofacial dysmorphism was present in 32 of 109 cases (30%) and all were associated with a syndrome of some type. Issues varied by syndrome, but included things such as mandibular malformation, cleft palate, and hypertelorism.

A neurologic abnormality was present in 30 of 109 cases (27%)—the most common findings being weakness, sensory loss, and spasticity. Other rarer findings included cerebral atrophy, occipital meningocele, bowel and bladder difficulty, seizures, and developmental delay.

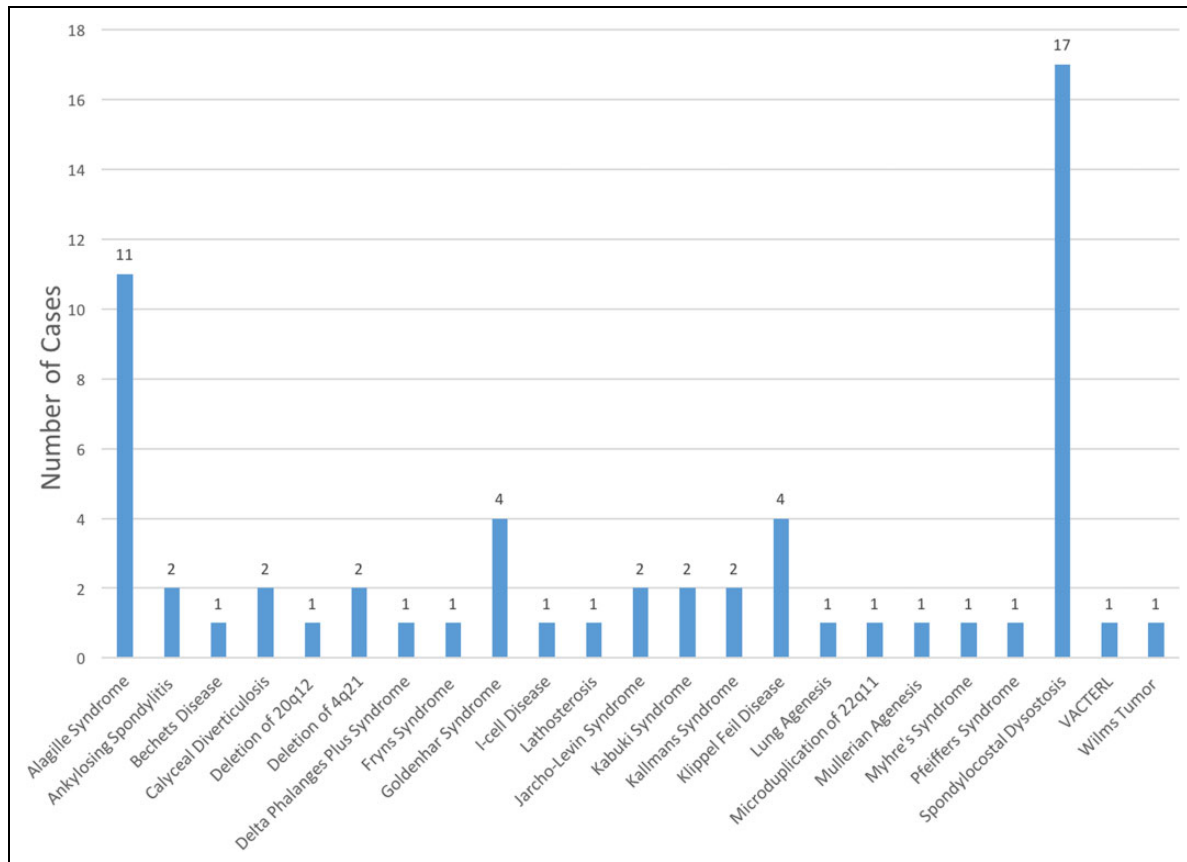


Figure 4. Summary of all syndromes that were associated with butterfly vertebrae.

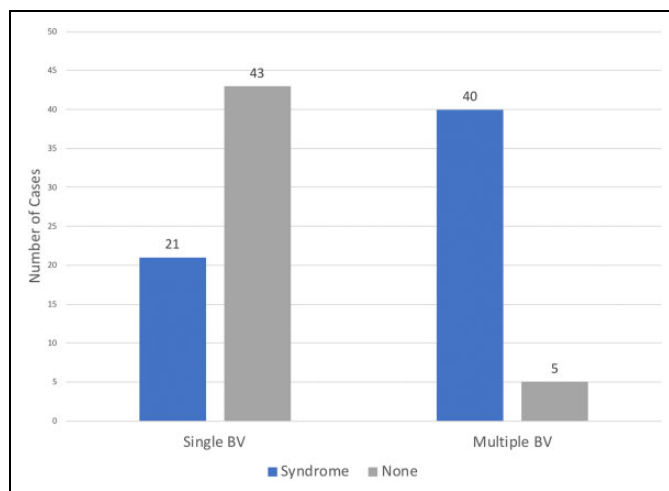


Figure 5. Breakdown of occurrences of single and multiple butterfly vertebrae either in isolation or as part of a syndrome. Multiple butterfly vertebrae were associated with the presence of a syndrome: ($P < .001$).

The cardiovascular system was affected in 25 of 109 cases (24%), the most common finding being pulmonary vein stenosis. Other cardiac abnormalities included patent ductus arteriosus, patent foramen ovale, coarctation of the aorta, mitral valve prolapse, dextrocardia, and cardiac hypertrophy.

The genitourinary system was affected in 25 of 109 cases (23%), with undescended testes being the most common finding, followed by a horseshoe kidney. Other common findings in this area were renal calculi, renal failure, absent, dysplastic, or hypoplastic kidneys.

The gastrointestinal system was involved in 24 of 109 cases (22%), the most common findings being biliary atresia/hypoplasia and jaundice; both of which are common findings in Alagille syndrome. Other findings included diaphragm defects, hepatomegaly, inguinal hernia, and anal atresia.

Laboratory values were abnormal in 17 of 109 of cases (16%), the most common abnormality being increased bilirubin and liver enzymes; again, related to Alagille syndrome.

Finally, the endocrine system was involved in 10 of 109 cases (9%), with thyroid abnormalities being the most common finding. A complete overview of associated conditions can be found in Figure 6.

Discussion

Butterfly vertebrae were first described in a 55-year-old man in 1850 by Rokitansky.⁵ The oldest case ever reported was in an archeological specimen in Sharuna, Egypt in the L3 vertebrae dated to 2150 BC.¹⁸ Since this time there have been many articles on butterfly vertebrae, mostly as incidental reports. We performed this study to synthesize all information available regarding this rare malformation, and to summarize its

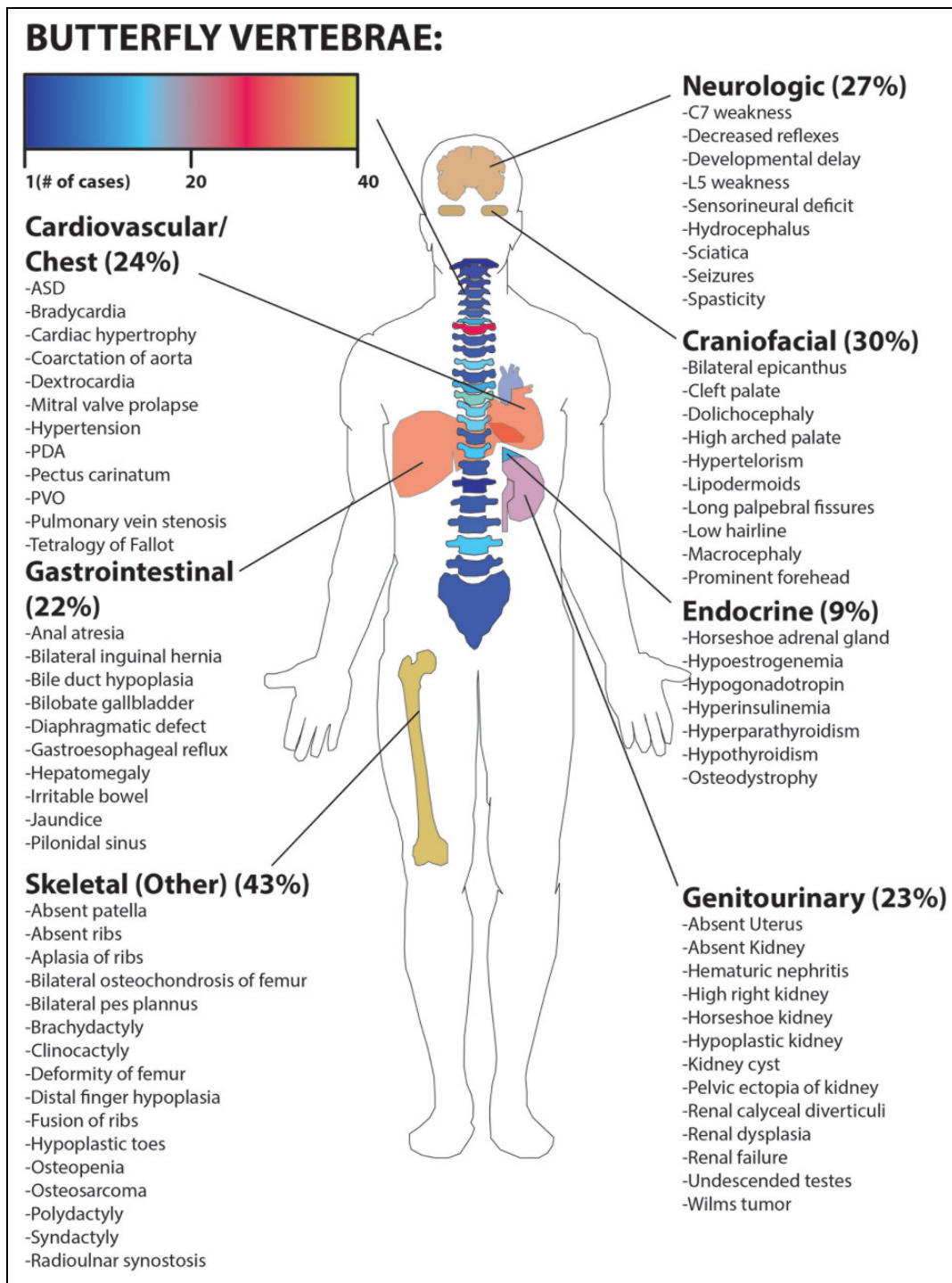


Figure 6. Summary of associated organ systems affected and specific problems.

associations. This study represents the largest collection of butterfly vertebrae to date.

Butterfly vertebrae occur as an aberration in the normal embryological development of the vertebral body. Ordinarily, the first stage of development of the spine is neurulation with the formation of the notochord at day 7 during gastrulation.¹⁹ This is followed by the migration of endodermal cells

and formation of the lateral mesoderm. Somatization of the mesoderm proceeds with the formation of 44 pairs of somites—blocks of tissue on either side of the neural tube.²⁰ The mesoderm is also responsible for the formation of cardiac, pulmonary, and renal tissue—hence the high association of vertebral anomalies with disturbances of other major organ systems.¹⁹ In this study, the associated abnormalities in the

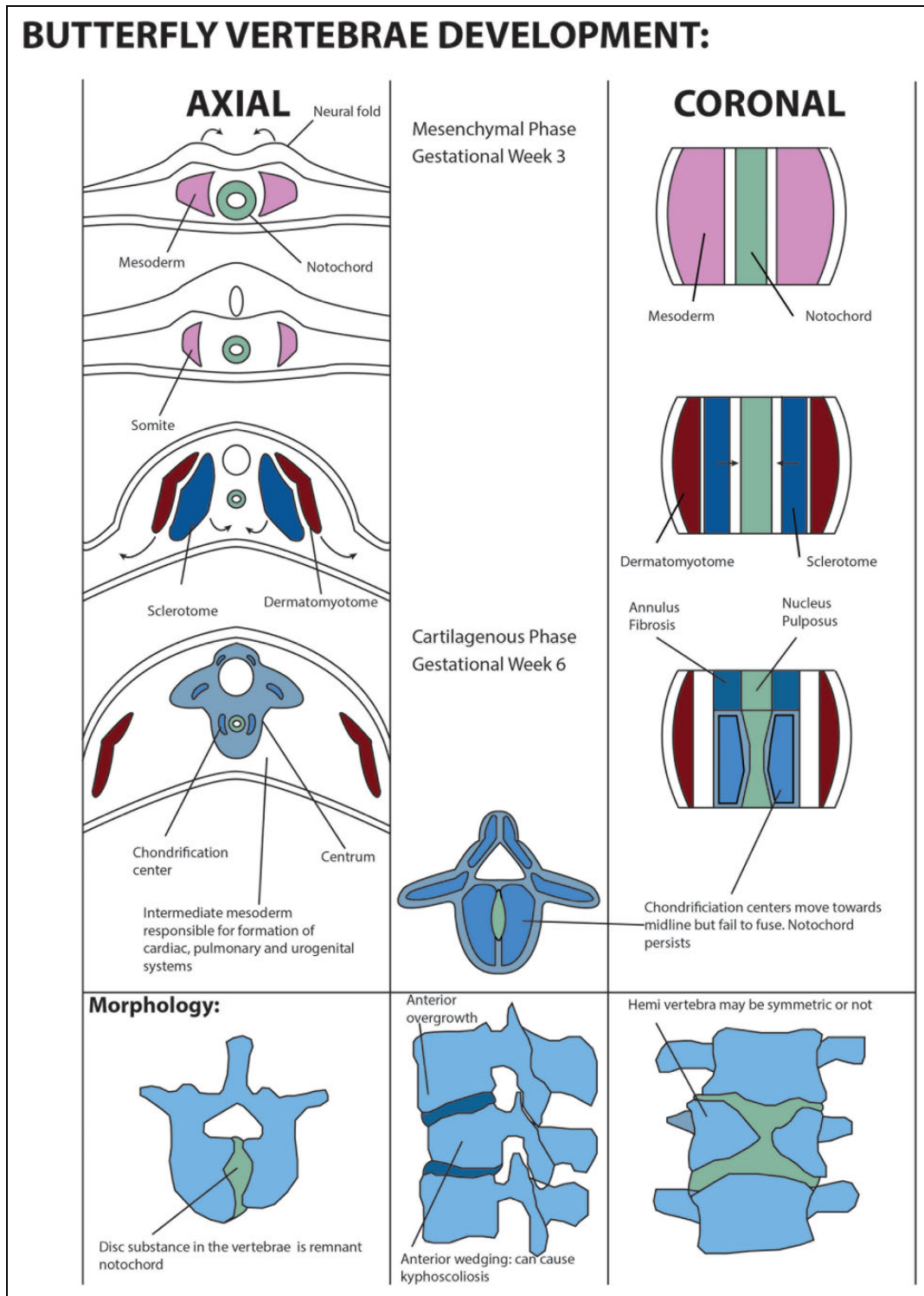


Figure 7. Development and morphology of butterfly vertebrae. Axial: development of the embryonic spine. Following formation of the notochord, the lateral mesoderm differentiates into somites, which form the dermatomyotome and the sclerotome. The sclerotome undergoes chondrification to form the vertebral body. Coronal: shows differentiation of the mesoderm into the dermatomyotome and the sclerotome. The notochord forms the nucleus pulposus.

cardiac, neurological, genitourinary systems were 30%, 27%, 23% respectively. Somites then differentiate into sclerotomes, which progress to form the spine and other aspects of the

skeleton, while dermatomyotomes form muscle. The close association between the development of the spine and the appendicular skeleton explains the high rate of butterfly vertebrae



Figure 8. Multiplanar reformatted computed tomographic image of a S1 butterfly vertebrae with associated sacral dysmorphism and pseudoarticulation on the left.

occurring with other skeletal defects. In this study, we noted that 43% of patients with a butterfly vertebra had another associated musculoskeletal abnormality. The sclerotomes then flank the notochord in the fourth week.²⁰ Two anterior sclerotomes undergo chondrification and fuse to become the cartilage vertebral body at week 6 while the third part becomes the posterior arch.²¹ The notochord is obliterated at the level of the vertebral body but persists at the disc level to become the nucleus pulposus.^{8,19} Ossification typically begins around week 12.

Spinal malformations occur generally under the headings of failure of formation, failure of segmentation, and neural tube defects.¹⁹ Butterfly vertebrae have been postulated to develop secondary to failure of formation. One theory is that during somatogenesis, the two lateral chondral centers simultaneously fail to fuse secondary to persistence of the notochord.^{2,8,22-24} (Figure 7). Hemivertebrae form through a similar process where a single chondrification center fails to migrate medially,

Table 2. Syndromes Associated With Butterfly Vertebrae.

Syndrome	Description
Alagille syndrome	An autosomal dominant disease characterized by a lack of the interlobular bile ducts, facial dysmorphism, pulmonary stenosis, posterior embryotoxon, and butterfly vertebrae (also known as arteriohepatic dysplasia). ²⁸ It may be asymptomatic and should be suspected in cases of butterfly vertebrae. ²⁸ In a case series of 92 patients with Alagille syndrome, butterfly vertebrae were present in 51% of patients. ²⁹
Ankylosing spondylitis	A chronic inflammatory arthritis typically affecting the sacroiliac joints. ³⁰
Behçet's disease	A systemic vasculitis associated with oral and genital ulcers as well as arthritis. ^{31,32}
Crouzon syndrome	A craniosynostosis syndrome associated with ocular proptosis and shallow orbits, as well as butterfly vertebrae. Anderson et al ³³ published the largest series reporting the spinal findings for this syndrome. In this series, 5 of 44 had evidence of cervical butterfly vertebrae. ³³ These results were not included in our current study as there was not enough patient data resolution to combine it with other cases.
Fryns syndrome	An autosomal recessive condition consisting of congenital diaphragmatic defect, abnormal facies, small thorax with widely spaced nipples, limb hypoplasia, hernia, and pulmonary hypoplasia. ³⁴
Goldenhar syndrome	A sporadic genetic disease that consists of a spectrum of auriculovertebral malformations including eye, ear, and vertebral anomalies. It is hypothesized to result from embryological disturbance of the ectoderm. ³⁵
Lathosterolosis	A defect in cholesterol synthesis that presents with multiple malformations, mental retardation, and liver pathology. ³⁶
Jarcho-Levin syndrome/ spondylocostal dysostosis	A spectrum of congenital malformations of the ribs and vertebrae with associated short stature. ³⁷⁻³⁹
Kabuki syndrome	A condition of unknown etiology with facial malformations that mimic the makeup worn in the Japanese Kabuki theater, mental retardation, and abnormal dentition. ⁴⁰
Kallman syndrome	A mutation in the FGFR-1 gene characterized by hypogonadotropic hypogonadism and anosmia. ⁴¹
Klippel-Feil syndrome	Congenital cervical synostosis of 2 or more vertebrae resulting from a mutation of the SGM1 gene causing fusion of cervical vertebrae. Clinical signs include low hairline, short neck, and limited range of motion of neck. ⁴²
Lung agenesis or pulmonary agenesis	A rare anomaly which may be associated with a number of other visceral systems abnormalities. ⁴³
Myhre syndrome	An autosomal dominant condition characterized by facial dysmorphism, short stature, muscle pseudohypertrophy, joint stiffness, and thickened skin. ⁴⁴
MURCS	Mullerian duct agenesis, renal agenesis, cervicothoracic somite dysplasia. ⁴⁵
Pfeiffer syndrome	A mutation of the type 1 and type 2 fibroblastic growth hormone causing craniosynostosis with broad thumbs and toes. ⁴⁶
VACTERL	Vertebral defects, anorectal malformations, cardiac defects, tracheoesophageal fistula with esophageal atresia, renal malformations, and limb defects. ⁴⁷
Other	22q11 micro duplications similar to DiGeorge syndrome, ⁴⁸ 20p12 insertional deletion, 4q21 deletion

and thus butterfly vertebrae can be thought of as adjacent hemivertebrae.^{2,19}

The geometry of butterfly vertebra is variable but tends to be deficient anteriorly, causing a wedge shape and focal kyphosis.²⁵ The 2 halves are typically equal but can be asymmetric, with an intact posterior arch and pedicles.^{5,26} In some cases, they may be connected by an isthmus of bone.⁵ They are typically cold on bone scintigraphy.²⁷ This structural abnormality has been proposed to alter the biomechanics of the spine and result in disc herniation (Figure 7).^{1,8,10} In this study, structural abnormality of the spine was the most common associated condition (70%), with scoliosis being the most common finding. Other common findings were other failure of formation and segmentation.

The thoracolumbar spine has been implicated as the most common location for the formation of butterfly vertebrae.^{2,6,9} McMaster et al²⁶ noted in their large series of 15 single butterfly vertebrae that the most common location was T11 at the thoracolumbar region.²⁶ This is in contrast to our findings, which showed T1 as the most common location. However, this finding was likely due to the high number of patients with spondylocostal dysostosis included in this report, which presents with upper thoracic and cervical abnormalities.

It is important to understand the radiographic features of butterfly vertebrae (see Figure 8 for a case example) to distinguish them from other pathological processes (fracture, metastasis infection, syringomyelia, and Charcot's disease).^{3,25} In this series, 10% of nonsyndromic patients were misdiagnosed as having a compression fracture. Close examination of the adjacent vertebrae will show features of long-standing deformity such as exaggerated elongation anterior margins to occupy the defect, and a normal intervertebral disc.²⁵ In addition, butterfly vertebrae typically cause less kyphosis than would be expected from the significant anterior wedging (Figure 7).³

Multiple previous reports have linked butterfly vertebrae with low back pain,^{1,7,9,11} the treatment of which is generally conservative. In this series, low back pain was the most common presenting complaint occurring in 23% of all cases and 30% of nonsyndromic cases. Nonetheless, it must be noted that the association between butterfly vertebrae and low back pain remains unproven as low back pain is a common presenting complaint in the spine patient population. The etiology of low back pain in a patient with butterfly vertebrae may be unrelated to the structural abnormality and thus requires further research. However, the treatment of low back pain in most instances was generally conservative, with one case report of progressive kyphosis which required instrumentation.²⁶ Butterfly vertebrae may also be associated with symptomatic disc herniation, which requires decompression.^{4,8,11}

Based on our findings, evaluation of the other organ systems should be performed in the presence of a butterfly vertebra, especially if they are multiple. In this study, there was a high association between the presence of multiple butterfly vertebrae and a syndromic presentation. 89% of cases which had >1 butterfly vertebrae were associated with the presence of a syndrome. However, a significant number of single butterfly vertebrae cases also presented as part of a syndrome (32% of

cases). Specific evaluation of the cardiac and genitourinary systems with ultrasound would be a practical and noninvasive modality to evaluate for any other malformations. Although there was a high incidence of neurologic abnormality in these cases, the description of these findings were reported based on symptoms as opposed to structural problems, and perhaps were unrelated directly to the butterfly vertebrae. Thus, the neurological system lacked a clear and cohesive group of associated findings due to lack of detailed information provided in the reports. Genetic testing should be considered in butterfly vertebrae patients who also have other skeletal or organ malformations. In this series, butterfly vertebrae were found to be associated with numerous syndromes surpassing those commonly cited in the literature (Table 2).

One of the weaknesses of this study is that the incidence of pathological findings associated with butterfly vertebrae may actually be higher than we report. In our review, system categories were marked as "not affected" if there was no specific mention in the case report of an abnormality which may actually have been present in the patient but was not reported by the authors. In addition, because of the review nature of this study, our report cannot demonstrate any causality with regard to low back pain, or neurological symptoms occurring with butterfly vertebrae.

In conclusion, this study represents the largest summary and synthesis of butterfly vertebrae cases to date. Isolated butterfly vertebrae may be associated with back pain, disc herniation, and spinal deformity. The presence of multiple butterfly vertebrae should raise suspicion for a greater systemic illness of syndrome and prompt diagnostic workup by the clinician. Knowledge of butterfly vertebrae are important not only to prevent misdiagnosis but also to ensure proper treatment of patients for suspected genetic abnormality.

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