Instability of the craniovertebral junction and treatment outcomes in patients with Down's syndrome

Derek A. Taggard, M.D., Arnold H. Menezes, M.D., and Timothy C. Ryken, M.D.

Operative intervention for the treatment of instability at the craniovertebral junction in patients with Down's syndrome has become somewhat controversial because some authors have reported high surgery-related complication rates and suggested that the incidence of neurological abnormality associated with this abnormal motion may be low. In this report, the authors describe the clinical and radiographic findings in 33 patients treated at their institution. Common presenting symptoms included neck pain (14 patients), torticollis (12 patients), and myelopathy manifested as hyperreflexia (21 patients), or varying degrees of quadriparesis (11 patients). Four patients suffered acute neurological insults, two after receiving routine general anesthetics for minor surgical procedures and two other patients following minor falls. Atlantoaxial instability was the most common abnormality documented on radiography (22 patients). Atlantooccipital instability (15 patients) was also frequently observed and was coexistent with the presence of atlantoaxial luxations in 14 patients. A rotary component of the atlantoaxial luxation was present in 13 cases. In 17 patients bony anomalies were present, the most frequent of which was os odontoideum (10 patients). Twenty-four patients underwent operative intervention, and successful fusion was achieved in 23. In six of nine patients with basilar invagination, reduction was achieved with preoperative traction and thus avoided the need for ventral decompressive procedures. There were no cases of postoperative deterioration, and 22 patients made excellent or good recoveries. The results of this series highlight the clinicopathological phenomena of craniovertebral instability in patients with Down's syndrome and suggest that satisfactory outcomes can be achieved with a low rate of surgical morbidity.

Key Words * Down's syndrome * craniovertebral junction * cervical spine * atlantoaxial instability * treatment outcomes

The most common chromosomal abnormality in man, trisomy 21, occurs approximately once in every 700 births. The clinical syndrome associated with this genetic aberration was originally described in 1866 by John Langdon Down and subsequently bore his name. Down's syndrome is well recognized by its phenotypic features, which include characteristic facies, hypotonia, ligamentous laxity, mental retardation, and transverse palmar creases. This disorder can variably affect nearly every organ system, resulting in numerous potential complications. Manifestations of the disease affecting the craniovertebral junction (CVJ) were first described in 1961 by Spitzer, et al.,[40] who reported on nine of 29 patients with atlantooccipital dislocations.
Surveys conducted of motion abnormalities at the CVJ have yielded a basic understanding of the various luxations for which patients with Down's syndrome have a propensity. We sought to update our own experience[27] with the treatment of instability of the CVJ in patients with Down's syndrome. The goal of the present study was to report on the incidence and associated clinical findings of the various abnormalities at the CVJ in patients with Down's syndrome. Furthermore, having established in this series a high rate of successful surgical outcomes, we wish to counter the misconception that the surgical treatment of these patients necessarily carries a high morbidity rate[8,18,29,35,38] and that they do not require surgical intervention when gross instability is found.[1,5,10,19,32,36]

CLINICAL MATERIAL AND METHODS

We reviewed the medical and radiographic records of patients with Down's syndrome who underwent treatment for abnormalities of the CVJ at the University of Iowa Hospitals and Clinics from May, 1976, to January, 1999. This did not include 48 other children with Down's syndrome who were evaluated for CVJ abnormalities but treated elsewhere. Demographic data obtained included age at presentation and sex of the patient. This included careful evaluation of history, neurological examination, and extensive neurodiagnostic imaging studies. Cervical spine radiography, pleuridirectional tomography, computerized tomography (CT) myelography, CT scanning with sagittal, coronal, and three-dimensional reconstruction, and magnetic resonance (MR) imaging were performed. Lateral flexion and extension radiographs of the cervical spine were obtained to determine the presence and degree of instability, as well as the extent to which the pathological process could be reduced. Pleuridirectional tomography as well as MR imaging was used to establish the effects of traction on the relationship of structure at the CVJ.

The presence of greater than 6 mm of predental excursion between the flexed and extended positions on a lateral cervical radiograph was considered abnormal in children less than 8 years of age.[21,22] The corresponding predental space in an adult was considered abnormal if greater than 3 mm.

Abnormal relationships among the basion, opisthion, tip of the dens, and anterior atlantal arch were used to define alantooccipital instability. The posterior arch of the atlas and orientation of the posterior mandibular ramus were also utilized. The numerous reference lines for occipitocervical dislocation were all used in determining the abnormality.[25]

Management decisions were influenced by the degree to which the compression could be reduced, location of neural compression when it could not be resolved, the craniovertebral architecture, and osseous maturation.[26] The primary goals of treatment were to stabilize patients whose neural compression could be reduced and provide decompression with stabilization in cases of irreducible neural compression. Irreducible compression pathology was decompressed in the manner in which encroachment occurred; in patients with ventral compression of the cervicomedullary junction (CMJ) a transoral decompressive procedure was performed, and those with dorsal compression were relieved via a dorsal route. In both cases, internal stabilization was performed after the decompressive procedure.

Treatment, including surgical and nonsurgical management, was then judged according to radiologically demonstrated and neurological outcome. Clinical outcomes were categorized at excellent (resolution of symptoms), good (improvement in symptoms), stable (no change or new deficit), or poor (worsened symptoms). In those patients in whom surgery was performed, fusion was considered complete when a mature fusion mass was visualized on lateral cervical radiographs and when abnormal motion on
RESULTS

The medical records of 33 patients were reviewed. The population was comprised of 21 male and 12 female patients whose average age was 16.7 years (range 3-49 years). The clinical findings at initial presentation are summarized in Table 1. Cervical or occipital pain, the most common presenting complaint, occurred in nearly half of the series (14 of 33 patients). Twelve patients presented with torticollis. Two patients had sustained acute neurological deficits after minor falls and another after receiving routine general anesthesia. Patients with CMJ compression presented with ataxia and progressive weakness. On examination hyperreflexia was revealed in a majority of patients (21 of 33), and 11 patients presented with varying degrees of quadriparesis.

<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUMMARY OF THE PRESENTING SIGNS AND SYMPTOMS IN 33 PATIENTS WITH DOWN’S SYNDROME AND CVJ INSTABILITY</td>
</tr>
<tr>
<td>Symptom</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>cervical pain</td>
</tr>
<tr>
<td>occipital pain</td>
</tr>
<tr>
<td>torticollis</td>
</tr>
<tr>
<td>acute injury after minor fall</td>
</tr>
<tr>
<td>anesthetic-associated injury</td>
</tr>
<tr>
<td>hyperreflexia</td>
</tr>
<tr>
<td>quadriparesis</td>
</tr>
<tr>
<td>gait ataxia</td>
</tr>
<tr>
<td>atrophy</td>
</tr>
</tbody>
</table>

Radiographic findings are highlighted in Tables 2 and 3. Atlantooccipital instability was demonstrated in 15 cases, and in 22 patients atlantoaxial instability was visualized on lateral flexion-extension cervical radiographs. Of the 15 patients with atlantooccipital instability, simultaneous instability at C1-2 was present in 12 patients, and had a fixed luxation at C1-2 was demonstrated in two. A fixed atlantoaxial luxation of greater than 3 mm was revealed in seven patients. Rotary luxation of the atlantoaxial joint was also common, occurring in 13 cases. In nine patients basilar invagination was displayed, in one a fixed atlantooccipital luxation was present, and in one subject C2-3 instability was demonstrated.

<table>
<thead>
<tr>
<th>TABLE 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUMMARY OF RADIOGRAPHIC FINDINGS</td>
</tr>
<tr>
<td>Finding</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>atlantooccipital instability</td>
</tr>
<tr>
<td>atlantoaxial instability</td>
</tr>
<tr>
<td>atlantoaxial fixed luxation</td>
</tr>
<tr>
<td>rotary atlantooccipital luxation</td>
</tr>
<tr>
<td>rotary atlantoaxial luxation</td>
</tr>
<tr>
<td>basilar invagination</td>
</tr>
<tr>
<td>bony anomalies</td>
</tr>
</tbody>
</table>

* In 12 patients there was coexistent atlantoaxial instability, and in two patients there was a fixed atlantoaxial luxation.
The bony anomalies of the occipitioatlantoaxial region were found in 17 cases are summarized in Table 3. An os odontoideum was discovered in 10 patients during radiological evaluation. In five patients hypoplasia of the posterior arch of C-1 was demonstrated, and os terminale, condylar hypoplasia, atlantal body hypoplasia, anomalous cervical facets, and atlantooccipital assimilation were found in one patient each. Two patients were additionally diagnosed as having juvenile rheumatoid arthritis.

Twenty-four patients underwent operative intervention for correction of a pathological process at the CVJ. Preoperative traction was applied in nearly all patients. Three patients, in whom compression caused by basilar invagination could not be reduced, underwent transoral odontoidectomy with dorsal occipitocervical fusion. Fifteen patients underwent dorsal occipitocervical fusion, with or without an atlantal decompressive procedure depending on the degree of posterior cervicomedullary compression. In nine patients fusion was performed from the occiput to C-2 (in one patient an additional unilateral C1-2 transarticular screw was placed), in seven patients from the occiput to C-3, and in one patient from the occiput to C-4. Three patients underwent atlantoaxial fixation, and in one patient a dorsal C1-3 fusion was performed after a failed C1-2 fusion had been performed at another facility. Eight patients were treated with cervical immobilization alone, and one 48-year-old patient with significant developmental delay and numerous medical problems received no intervention for an asymptomatic, fixed atlantoaxial luxation, which was unchanged during a 6-month period.

A summary of clinical outcomes is provided in Table 4. No patient worsened after either conservative or operative intervention. Twelve patients were judged to have excellent results based on resolution of their symptoms. Ten were considered to have made a good outcome as symptoms improved with therapy. In 11 patients a stable result was demonstrated because they either remained asymptomatic or sustained no new deficits. In 20 of the 21 patients in whom a minimum of 6 months of radiographic follow up was performed, fusion was successfully achieved. In one patient with severe psychomotor retardation, who was poorly compliant with a cervical collar after undergoing an occiput-C3 fusion in which a stainless steel loop, cables, and rib graft were placed, a fibrous union at C1-2 was displayed.
Two cases of postoperative wound infection were treated with intravenous antibiotics. One of these wounds dehisced and was allowed to heal by secondary intent. One patient with poor preoperative pulmonary function required a tracheostomy for failure to wean from ventilatory support and subsequently died of unknown causes 3 months postoperatively in a rehabilitation facility. Halo pin-site infections were not uncommon but were not considered a significant complication.

**Illustrative Cases**

**Case 1**

This patient was a 4-year-old girl with Down's syndrome who, while playing, fell off a couch and landed on her head in a flexed position. Her mother noted immediately that the girl cried appropriately but that her upper and lower extremities were flaccid. On transfer to our institution she had flaccid upper extremities and lower extremity movement graded, as 3/5 bilaterally. Extensor response to plantar stimulation was noted bilaterally.

On MR imaging performed during the acute phase postinjury (Fig. 1 upper left) a contusion at the CMJ as well as an increased predental space were demonstrated. A significant atlantoaxial subluxation was also observed (Fig. 1 upper right). Bony anomalies included a dystopic os odontoideum and hypoplastic posterior atlantal arch as shown in Fig. 1 lower. She was immobilized in a cervical collar and received an appropriate course of intravenous methylprednisolone. Subsequently, she underwent dorsal occiput-C4 fusion in which contoured titanium loop and autologous rib graft were placed. At 3-month follow-up examination, she was ambulatory, experienced no focal motor deficits or hyperreflexia, and radiography revealed a maturing fusion.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>excellent</td>
<td>12</td>
</tr>
<tr>
<td>good</td>
<td>10</td>
</tr>
<tr>
<td>stable</td>
<td>11†</td>
</tr>
<tr>
<td>poor</td>
<td>0</td>
</tr>
</tbody>
</table>

* Twenty-four patients underwent operative intervention and nine patients received conservative treatment.
† One patient was improving neurologically when he died of unknown causes in a rehabilitation facility 2 months after surgery.
Case 1. Imaging studies obtained in a 4-year-old girl after a minor fall resulted in acute quadriplegia. Upper Left: Sagittal T2-weighted MR image revealing an abnormal atlantoaxial interval of 8 mm and hyperintense signal at the CMJ consistent with contusion. Upper Right: Lateral cervical radiograph revealing a grossly subluxated atlantoaxial segment. Lower: Sagittal reconstruction of a CT scan obtained at the occiput-C3 revealing a dystopic os odontoideum and an increased predental space, as noted on the MR image. The posterior atlantal ring is not visualized because the bifid posterior arch of C-1 was shown as well.

Case 2

This patient was a 7-year-old boy with Down's syndrome in whom a history of upper respiratory infections and otitis media had begun 2 months prior to presentation, which was prompted by complaints of neck pain. His neurological exam was significant for demonstrating severe developmental delay and hyperreflexia of the lower extremities. A CT scan of the CVJ revealed a dystopic os odontoideum,
occipitoatlantoaxial luxations, as well as a bifid posterior arch of C-1 (Fig. 2).

Fig. 2. Case 2. Sagittal reconstruction of a three-dimensional CT scan obtained in a 7-year-old boy with recent upper respiratory infections, neck pain, and hyperreflexia, revealing mild atlantooccipital malalignment. Also of note is a dystopic os odontoideum and increased atlantoaxial interval. The posterior ring of C-1 is hypoplastic.

The patient underwent a dorsal occiput-C3 fusion in which a titanium contoured loop and autologous rib graft were used; postoperatively he was immobilized in a halo vest for 6 months, which resulted in an excellent fusion and resolution of his neck pain and hyperreflexia.

Case 3

This patient was an 8-year-old boy who developed, as noted by his parents, a leftward head tilt, which was evident on examination. Additionally, the patient experienced mild hyperreflexia of the lower extremities. Dynamic lateral cervical radiographs revealed 10 mm of antlantooccipital instability (Fig. 3 left and center). The patient underwent a dorsal occiput-C3 fusion in which titanium contoured loop and autologous rib graft were used; postoperatively he was immobilized in a halo vest for 3 months and subsequently a cervical collar. At 1-year follow-up examination, a radiograph (Fig. 3 right) revealed that a mature bone graft had been incorporated into the occiput and posterior cervical elements.
Fig. 3. Case 3. Radiographic studies obtained in an 8-year-old boy with a leftward head tilt and mild hyperreflexia. Preoperative flexion (left) and extension (center) lateral cervical radiographs showing nearly 10 mm of atlantooccipital instability. A normal atlantoaxial relationship is maintained. Right: Follow-up lateral radiograph obtained 1 year postoperatively revealing intact instrumentation as well as a mature fusion mass that has incorporated the occiput and posterior cervical elements.

DISCUSSION

In 1961 Spitzer, et al.,[40] provided the first description of atlantooccipital luxation and atlantal hypoplasia in Down's syndrome. In 1965, evidence of pathological motion at the atlantoaxial segment in these patients was defined by Tishler and Martel.[41] The initial case of symptomatic atlantoaxial subluxation as well as successful reduction and fusion was reported the following year.[9] Since that time, a significant body of literature has developed in which the pathological entities of the CVJ in patients with Down's syndrome are described.

The generalized ligamentous laxity associated with Down's syndrome, as well as incidence of bony anomalies, predisposes the CVJ to instability because of the complex interaction of ligamentous and bony anatomy required to maintain stability. In 7 to 40% of patients with Down's syndrome there is radiographic evidence of atlantoaxial instability,[1,20,22,28,33,36] although the incidence of symptomatic instability may be less than 1%.[1,20,27,31,32] Atlantooccipital instability and rotary luxation of the atlas are well described in patients with Down's syndrome and should not be overlooked.[11,27,33,37,39,44] Parfenchuck, et al.,[30] have suggested that the incidence of posterior atlantooccipital hypermobility in Down's syndrome is 8.5%. Bony anomalies such as os odontoideum and hypoplasia of various craniovertebral elements, including the atlantal ring and condyles, likely increase the risk for instability at the CVJ.[3,4,6,10,14,15,22,23,33,36,37,39,40] This evidence, in part, prompted the American Academy of Pediatrics Committee on Sports Medicine and Fitness to mandate that participants with Down's syndrome undergo physical examination and screening cervical spine radiography prior to competition in the Special Olympics in 1983.
Evidence regarding the natural history of atlantoaxial instability suggests that it may be a progressive disease. In following 33 cases over a 13-year period, seven patients were found to develop instability (predental space of more than 5 mm) as compared with only one patient in whom this instability was present at the start of the study.[6] Two patients underwent arthrodesis and one died of the pathological process. Pueschel, et al.,[32] evaluated 95 cases over a 3- to 10-year period and found that in seven patients a predental space of greater than 5 mm had developed. These authors claimed that none of the patients became symptomatic. Ferguson, et al.,[13] have recently called into question the relationship of neurological abnormality and atlantoaxial instability. Eighty-four patients with Down's syndrome were evaluated for a predental space of 4 mm or greater or 2 mm of translation in flexion-extension. In 20% (17 patients) instability at the atlantoaxial joint was demonstrated. In a comparision of results of neurological examinations between patients in whom subluxation was present with those in whom it was not, no significant difference could be found relative to incidence (29% and 27%, respectively) or type of positive neurological finding. Results of our series demonstrate not only that children with this phenomenon are predisposed to neural compromise but also a high rate of neurological recovery.

Antlantooccipital and occipitoatlantoaxial instability are expected findings in the Down's syndrome population.[11,17,24,30,42,43] Clinical correlations were not made in the first description of antlantooccipital luxation by Spitzer, et al.[40] Neurological abnormalities have been found in up to 66% of patients with antlantooccipital pitoatlantal instability.[30] In a prospective review of 64 patients with antlantooccipital instability, 61% of the patients were shown to have a posterior occipital subluxation greater than 4 mm and 21% to have a predental space of greater than 5 mm.[42] Uno, et al.,[43] reviewed flexion-extension cervical radiographs obtained in 75 patients with Down's syndrome and found a significant number of patients in whom antlantooccipital hypermobility was demonstrated when compared with 30 age-matched controls. Furthermore, they found occipitoaxial instability coexistent with atlantoaxial instability in all cases. In 11 of the 14 patients in our series, atlantoaxial instability along with antlantooccipital instability were found, which supports this finding, although correlation is not absolute. In this light, both Brooke, et al.,[5] and El-Khoury, et al.,[11] have reported two patients with Down's syndrome in whom antlantooccipital instability was present without atlantoaxial abnormality.

Rotary luxations of the antlantooccipital and atlantoaxial joint were initially described in a Down's syndrome patient in 1969 by Sherk and Nicholson.[37] Surgical intervention was not undertaken, and 9 years after the diagnosis was made this female patient developed acute quadriplegia and died of respiratory failure. Other investigators have recognized a rotary component of instability in some patients with Down's syndrome.[7,12,33,44] In over one third of the patients in our series a component of rotary luxation at C-2 was found, and in and one patient a rotary luxation at occiput-C1 was demonstrated. It is important to recognize this phenomenon as it is in any situation, because the ipsilateral vertebral artery can kink and the contralateral vessel put on stretch as the rotation at C1-2 exceeds 35°.[25] Subsequently, the facets may lock and result in a fixed luxation and can only be disengaged if traction and derotation are performed. One must recognize that this rotary component can worsen the canal compromise and increase the stress placed on the cruciate ligament and, thus, can worsen the stability of an already compromised CVJ in a patient with Down's syndrome.

In our series clinical presentation was precipitated by upper respiratory infection in five patients. An understanding of the embryology and anatomy of the region can serve to explain this association. A single embryological unit forms the synovial membrane of the entire occipitoatlantoaxial complex. The upper jugular digastric chain serves as the site of lymphatic drainage for both the CVJ and the
nasopharynx and the paranasal sinuses. Infection of the latter can proceed retrograde into the CVJ and result in hyperemia, synovial inflammation, joint effusion, and further ligamentous laxity.

The bony anomalies associated with Down's syndrome, particularly os odontoideum, deserve emphasis. Unsuspected fractures of the odontoid, with secondary pull of the alar and apical ligaments, may result from repeated minor traumatic events in these patients. Over time, the cruciate ligament becomes incompetent, resulting in atlantoaxial dislocation and possibly allowing for compression at the ventral CMJ because the odontoid ascends into foramen magnum. The development of a new ossicle at the ventral CVJ in a 12-year-old patient, which was not seen on a radiograph when the patient was 6 years of age, was described in 1969.[37] Other similar descriptions followed[14,15,23] and in 1985 Braakhekke and colleagues[4] described 20 patients in whom myelopathy had developed secondary to atlantoaxial instability; in nine of these patients either an os odontoideum or odontoid hypoplasia was present.[4] Pueschel, et al.,[33] have provided evidence that a higher rate of cervical bony anomalies exists in the subgroup of Down's syndrome patients in whom atlantoaxial instability is present (31 of 39) compared with those in whom instability is not present (14 of 39).[33] In this report the authors also reviewed the bony anomalies in Down's syndrome patients, and os odontoideum and ossiculum terminale were shown to be common. This evidence supports the findings in our series of nearly half the patients in whom bony anomalies were identified, the most common being os odontoideum followed by posterior atlantal arch hypoplasia.

In the clinical setting, achieving consistent, successful outcomes in this patient population is challenging. Incomplete evaluation or understanding of the complex interactions at the CVJ has resulted in poor pre- and perioperative planning and treatment, including failure to recognize simultaneous instability at the different segments of the CVJ,[18] failure to obtain proper reduction prior to the decompressive and fusion procedure,[38] and performing intraoperative reduction without application of traction.[29] In our own clinical experience, we have seen fusion failure as a result of inappropriate postoperative immobilization, failure to recognize and appropriately treat ventral pathological processes, and inadequate bone grafting. Segal, et al.,[35] have reported successful initial fusion in only two of 10 patients and bone graft absorption in six patients.[34] More recently, in 7 of 15 patients with Down's syndrome a nonunion occurred after attempted posterior arthrodesis.[8] In this series reported by Doyle, et al.,[8] four of the seven patients achieved solid bony fusion after reoperation; in three of these four patients, fusion was preceded by loss of reduction and neurological deterioration and successful fusion was achieved only after incorporation the occiput on the second attempt.

Abnormal physiological processes in the Down's patient may also contribute to poor outcome. The T-cell-dependent processes of the immune system in patients with Down's syndrome are deficient as measured both quantitatively and qualitatively. The overall number of T lymphocytes is decreased as is the synthesis of lymphokines and the secretory products of these cells. These products may affect the initial inflammatory stages of bone graft incorporation.[4,16] Other authors have implicated a collagen defect intrinsic to Down's syndrome patients as responsible for bone graft resorption and poor graft maturation.[2,35] The sequential forms of collagen required for successful graft incorporation may be deficient and thus contribute to nonunion or graft absorption.

Based on our own series and our interpretation of the literature, we find that occipitocervical fusion is required to address cranial settling appropriately, reducible basilar invagination, and anterior, posterior, or lateral cranial dislocation within the CVJ.[25] This is performed in as far lateral an interlaminar fashion as possible between the axis and atlas. Although iliac crest may be harvested, we favor the use of
autologous full-thickness rib as the donor bone. Sawin, et al.,[34] have shown that posterior rib harvesting was not associated with significant pulmonary morbidity when compared with autologous iliac crest harvesting in patients undergoing cervical fusion procedures. Furthermore, rib grafting was associated with an excellent fusion rate in their series. Titanium cable is used to purchase the exoccipital bone to improve the stiffness of the construct. Generally, patients are immobilized in a halo vest for 3 to 4 months for atlantoaxial fusion and up to 6 months for atlantooccipital fusion. Inadequate immobilization invites nonunion, resorption of the graft, and progressive instability.[25,39]

CONCLUSION

In this review we emphasize types of instability at the CVJ in patients with Down's syndrome. Most frequently, instability is seen at the atlantooccipital and atlantoaxial articulations and commonly occur simultaneously. Rotary luxations, particularly of the atlantoaxial joint, are also common and should be corrected. Os odontoideum is the most common bony anomaly and likely results from repeated minor trauma. Our results indicate that an excellent rate of successful fusion can be obtained, with thoughtful consideration of the pathological processess present as well as appropriate perioperative planning and postoperative immobilization.

References


Manuscript received April 18, 1999.

Accepted in final form May 18, 1999.
Address reprint requests to: Arnold H. Menezes, M.D., Division of Neurosurgery, University of Iowa Hospitals and Clinics, Iowa City, Iowa 52242.