Congenital cranial dysinnervation disorders (CCDDs)

The term congenital cranial dysinnervation disorder (CCDD) was introduced by Gutowski et al. in 2003 to describe strabismus conditions that result from developmental error in innervation of some of the extraocular muscles. Examples of these conditions include Duane's syndrome and congenital fibrosis of the extraocular muscles. These originally were thought to be mechanical, but now we know that the aetiology is a congenital abnormality in innervation.

In this article I will summarise and discuss some of the common types, their features, and some management options.

Features:

This group of conditions are present from birth, and it is a non-progressive disorder. The original issue is an abnormality in the development of the brain stem or the cranial nerves.

There are two types of dysinnervation that feature in these disorders:

- **Primary dysinnervation:** reduction or absence of normal innervation to an extraocular muscle. This leads to muscle paresis and fibrosis.
- **Secondary dysinnervation:** paradoxical innervation of that muscle by branches from another cranial nerve. This leads to co-contractions or up and down shoots.

Classification:

These disorders can be classified depending on the cranial nerves involved in the primary dysinnervation:

- **Third nerve and fourth nerve:** these will lead to congenital fibrosis of the extraocular muscles (CFEOM).
- **Sixth nerve and seventh nerve:** these will lead to Duane's syndrome, Mobius syndrome, horizontal gaze palsy with progressive scoliosis (HGPPS) and congenital facial nerve palsy.

Duane's syndrome:

This is a congenital disorder that has been described in detail by Duane. It is usually unilateral in about 80% of cases, but could be bilateral and asymmetric. It is more common in females, and more common in the left eye than the right.

It is caused by absent or deficient sixth cranial nerve, so the lateral rectus muscle gets innervated by branches from the third nerve. There is some evidence that parts of the lateral rectus muscle still get some innervation from the sixth nerve fibres if they are present, while other parts have innervation from the third nerve and a denervated portion which becomes atrophic and fibrotic.

This could explain the various levels of abduction limitation in Duane's patients. It also explains other features of the syndrome motility pattern. The co-contraction on the medial rectus and the lateral rectus will lead to some limitation of adduction. The abduction is limited due to poor innervation from the sixth nerve. The co-contraction will also explain the globe retraction and the up and down shoots.

Although most cases are sporadic, up to five percent could be familial suggesting a possible genetic element.

Classification:

1. **Brown's classification:**
   a. Type A: limited abduction, less limitation to adduction (the original Duane's).
   b. Type B: limited abduction with normal adduction.
   c. Type C: limited adduction with less limitation of abduction with exotropia.
2. **Huber's classification:**
   a. Duane type I: severe limitation of abduction (with widening of the palpebral fissure on attempted abduction) and normal or minimal limitation of adduction (with narrowing of the palpebral fissure and globe retraction on adduction).
   b. Duane type II: severe limitation of adduction and normal or minimal limitation of abduction (reverse of type I).
   c. Duane type III: limitation of both adduction and abduction.

Features:

1. **Limitations of horizontal eye movements:** depending on the type, this is usually abduction and to a lesser degree adduction in type I.
2. **Abnormal head posture:** this is usually adopted to centralise the field of binocular single vision. The most common posture is a face turn towards the affected side (in type I) but in other types such as type II with exotropia, a face turn to the unaffected side could be present.
3. **Strabismus in primary position:** this is usually a small esotropia in type I (despite the presence of a large limitation of abduction) but could be exotropia especially in type II. It is usually incomitant, especially in unilateral cases. There might be some vertical deviation especially in bilateral cases.
4. **Globe retraction:** this happens on adduction accompanied with narrowing of the palpebral fissure due to the co-contraction of the horizontal rectus muscles.
5. **Up shoots and down shoots:** these happen on adduction and could be mechanical or innervational in origin.
   a. Mechanical: due to slippage of the globe around the tight lateral rectus muscle.
   b. Innervational: these are less common, gradual in nature and thought to be related to co-innervation of the lateral rectus and the vertical rectus muscles.
6. **Binocular single vision:** majority of patients would have a degree of stereopsis in primary position.
7. **Absence of diplopia:** majority of patients don't complain of diplopia, although some are aware of it on side gaze.
8. **Systemic features:** around a third of patients would have some systemic developmental anomalies involving various organs.

Differential diagnosis:

1. **Simulated Duane's syndrome:**
   a. Trauma such as medial orbital blow out fracture
   b. Orbital disease such as myositis or infiltrative conditions
   c. Iatrogenic from extensive resection to the horizontal rectus muscles.
2. **Mobius syndrome:**
   a. Usually, bilateral facial nerve palsy and limitation of abduction
   b. Other lower cranial nerves can be involved.

3. **Congenital sixth nerve palsy:**
   a. Very rare
   b. Large angle esotropia in primary position matching the limitation of abduction
   c. No limitation to adduction
   d. No changes to palpebral fissure or globe position
   e. No up shoot or down shoot.
4. **Infantile esotropia:**
   a. Large angle alternating esotropia in primary position
   b. Abduction can be demonstrated by unilateral occlusion or passive head movements
   c. No changes to palpebral fissure or globe position
   d. No up shoot or down shoot.

Surgical management of Duane's syndrome:

1. **Indications:**
   a. Large manifest strabismus in primary position
   b. Symptoms such as diplopia
   c. Large abnormal head posture
   d. Severe globe retraction or up / down shoots.
2. **Aims:**
   a. Correct manifest deviation in primary position
   b. Centralise the field of binocular vision and possibly expand it
   c. Reduce the abnormal head posture
   d. Reduce the retraction or the vertical imbalance.
3. **Surgical options:**
   a. These include horizontal rectus muscle recessions or vertical muscles transposition.
   b. In Duane type I with esotropia:
      i. Depending on the angle in primary position and the results of the intraoperative force duction test (FDT): ipsilateral or bilateral medial rectus (MR) recessions +/- contralateral MR posterior fixation suture (Faden).
      ii. Transposition of the vertical rectus muscles temporally. This could improve abduction and increase the area of binocular single vision. This could be combined with recession of the ipsilateral medial rectus muscle (if the force duction test is positive indicating contracture) or with a Foster's augmentation sutures.
   c. In Duane type II with exotropia:
      i. Usually, will need a recession of the ipsilateral lateral rectus muscle.
   d. Surgery for the up and down shoots on adduction:
      i. Mechanical: recession of the ipsilateral lateral rectus muscle or Y-splitting of the lateral rectus muscle.
      ii. Innervational: recession of the relevant vertical rectus muscle.

Congenital fibrosis of the extraocular muscles (CFEOM):

This is a spectrum of conditions where the pathogenesis is a change in the innervation of the extraocular muscles leading to secondary fibrosis. There are several classifications based on the clinical features or based on the genetic analysis.

Classification:

1. **Generalised fibrosis syndrome:** common and most severe type with fibrosis of all extraocular muscles and loss of all ocular motility, bilateral ptosis, chin up head position and eyes fixed in down gaze.
2. **CFEOM type 1:** bilateral ptosis and limitation of elevation, autosomal dominant.
3. **CFEOM type 2:** exotropia with limitation of adduction and vertical muscle imbalance, autosomal recessive.
4. **CFEOM type 3:** unilateral or bilateral ptosis with various extraocular muscles involvement (muscles of the III nerve), autosomal dominant.
5. **Strabismus fixus:** eyes fixed in side gaze with no horizonal movements but preserved vertical movements with marked esotropia or exotropia.

Differential diagnosis:

a. Partial third nerve palsy
b. Double elevator palsy
c. Mobius syndrome
d. Brown syndrome
e. Orbital floor fracture
f. Thyroid eye disease
g. Chronic progressive external ophthalmoplegia (CPEO)
h. Myasthenia gravis (MG).

Surgical management:

This is a challenging situation and likely to need more than one procedure. Intraoperative force duction testing can provide some guidance. Vertical imbalance usually needs addressing prior to horizontal imbalance, and most cases would require unilateral or bilateral asymmetric recession of the inferior rectus muscles. Large recessions might be needed, but risk creating limitation of depression or lower lid retraction. Transposition of the horizontal muscles superiorly (Knapp procedure) might be needed as a secondary procedure.

Mobius syndrome:

There is a spectrum of features which are commonly bilateral:

1. Facial nerve palsy
2. Limitation of abduction due to any of the following:
   a. Horizontal gaze palsy
   b. Sixth nerve palsy
   c. Duane's syndrome
   d. CFEOM
3. Lower cranial nerves involvement (9th - 12th) with swallowing and speech difficulties
4. Other systems involvement and mental development delay.

Surgical management usually include large medial rectus recessions to improve the position of the globe in the primary position.

Summary

CCDDs are a group of complex, congenital, non-progressive disorders. It is important to recognise these patterns as it spares lots of patients' anxiety, and reduces the need for unnecessary investigations.

Management of complex strabismus resulting from these conditions requires a high level of skill and knowledge of the effects of each of the above suggested procedures, and possible direct and indirect consequences.

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