Nelson's Syndrome

Pathophysiology\[1\]

Nelson's syndrome is a potentially life-threatening condition which occurs when an adrenocorticotropic hormone (ACTH) secreting tumour develops following therapeutic total bilateral adrenalectomy (TBA) for Cushing's disease. First described in 1958, it can develop as long as 24 years post-TBA but the mean is 15 years.\[2\] When the first cases were described the mortality rate was 12% but this has improved with earlier diagnosis and better management.

Cushing's disease is the name given to a pituitary adenoma that secretes ACTH, also called a corticotrophinoma. Such patients have high levels of cortisol which suppress the production of corticotrophin-releasing hormone (CRH) from the paraventricular nucleus of the hypothalamus. The normal cortisol feedback mechanism of the hypothalamo-pituitary-adrenal (HPA) axis is thus disturbed, with loss of circadian rhythm, and excess cortisol production. Cushing's disease is treated by curative trans-sphenoidal surgery (TSS).\[3\] However, if this is not possible (for example, if the corticotrophinoma is undetectable, surgically unresectable or when it has recurred following previous TSS), adrenalectomy is an option. TBA is usually curative with cortisol levels quickly returning to normal following surgery but its use is limited by the potential for developing Nelson's syndrome.

The pathophysiology of Nelson's syndrome and the factors leading to its development are poorly understood. It has previously been proposed that it develops due to release of the negative feedback that would otherwise suppress high cortisol levels, in turn leading to restoration of CRH production by the hypothalamus going on to stimulate corticotroph neoplasia. However, although this has been seen in animal studies, human evidence is lacking. Also not all patients post-TBA go on to develop Nelson's syndrome and most who do have adequate exogenous steroid replacement therapy. The corticotrophinomas of Nelson's syndrome and Cushing's disease are histologically and molecularly similar and it would appear that patients with Cushing's disease who have the more aggressive subtypes of corticotrophinoma are more likely to develop Nelson's syndrome; Nelson's tumours tend to be more invasive and more likely to be macroadenomas than those of Cushing's disease.

The signs and symptoms of Nelson's syndrome derive from the effects of raised ACTH and pressure of the tumour on surrounding structures, inhibiting release of other pituitary hormones.

Epidemiology\[1\]

Nelson's syndrome is rare. Epidemiological information is sparse but the available data suggest that the incidence is falling and that modern treatments are helping to reduce morbidity and mortality, including the use of high-resolution MRI and more sensitive ACTH measurements to monitor patients post-TSS.\[4\] Even in early series, only 20-40% of patients with a pituitary adenoma who had bilateral adrenalectomy developed Nelson's syndrome. Reported rates of later studies vary from 8-29%.\[3\]

Risk factors

- Rapid rise in ACTH post-TSS; a high ACTH level one year after adrenalectomy is thought to be predictive of corticotroph tumour progression.
- Longer duration of Cushing's disease prior to adrenalectomy.
- Younger age; children are at particularly high risk.
- Lack of cortisol suppression demonstrated on high dose of dexamethasone test prior to TSS may be predictive of later Nelson's syndrome.

Raised urinary cortisol levels prior to adrenalectomy are not predictive of developing Nelson's syndrome. Insufficient exogenous steroid following TBA is also no longer thought to be a risk factor.
Presentation[1]

History - early presentation
- Hyperpigmentation occurs in up to 42% of people even when diagnosed early, due to the action of ACTH on melanocytes.
- Visual field defects occur in 10-57% and should be enquired about. They may be too insidious to have been noticed and formal testing may be required.

History - late presentation
- Headaches are common with pituitary tumours and are probably the result of stretching of the diaphragma sellae. Features of raised intracranial pressure occur late and are uncommon because they require a tumour large enough to obstruct the flow of cerebrospinal fluid (CSF).
- Hypopituitarism occurs when the hypothalamic-pituitary portal system is disrupted or normal pituitary tissue is destroyed by the tumour:
  - It may be partial rather than total. The anterior pituitary is more often involved than the posterior pituitary.
  - Often hormone deficiency is incomplete.
  - In children and adolescents, note growth and age of puberty. Cushing's syndrome often slows growth in children but operation should return it. If not, investigation is required.
  - In all patients, enquire for symptoms of polyuria and polydypsia (due to diabetes insipidus), hypothyroidism and presence of galactorrhoea.
  - In women, amenorrhoea may be the first sign of pituitary disease. Galactorrhoea is uncommon in men but hyperprolactinaemia is a cause of erectile dysfunction.
- Testicular pain. During embryogenesis, adrenal cortical cells may migrate along the line of gonadal descent and may even be sequestered in the hilum of the testes, producing adrenal rest tissue. In Nelson's syndrome, this adrenal rest tissue may become stimulated and, if in the testes, it can cause testicular pain and oligospermia. Rarely, the adrenal rest tissue can produce enough cortisol to produce normal levels or even cause recurrence of Cushing's syndrome.
- The tumour may also cause diplopia and cranial nerve lesions by involving the oculomotor, trochlear and abducens nerves and also the ophthalmic branch of trigeminal. Visual symptoms or signs depend upon where the tumour presses.

Examination
- In children and adolescents, note height and weight.
- Hyperpigmentation is usually obvious. A linea nigra is often apparent. This is a dark line from the pubis to the umbilicus. Scars and areolae are pigmented and, as with Addison's disease, pigmentation is more marked in the creases of the hands. Some patients develop hyperpigmentation after bilateral adrenalectomy but do not develop full-blown Nelson's syndrome.[5]
- In adolescents there may be features of delayed puberty.
- Check eye movements, as the external ocular muscles will be affected if the III, IV or VI cranial nerves are involved. Damage to the ophthalmic division of the trigeminal nerve will impair sensation over the forehead and perhaps corneal reflex.
- Check the fundi, including looking for papilloedema.

Investigations[1]
The diagnosis of Nelson's syndrome depends on raising levels of ACTH in the presence of an enlarging pituitary tumour post-TBA. Whether or not hyperpigmentation has to be present is controversial.

- ACTH will be very markedly elevated. The cutoff is controversial but a level of >500 ng/L plus progressive elevations of ACTH has been proposed. ACTH should be measured at 8 am prior to routine steroid administration. One study found that a plasma ACTH concentration above 154 pmol/L occurred only in the subjects with Nelson's syndrome.[8] The ACTH response to CRH is also enhanced but this is not necessary for diagnosis.
- MRI or CT to identify an expanding pituitary mass when compared with scan prior to TBA surgery. MRI is useful, both for detection and to monitor progression of a microadenoma. Experience is, however, required in interpretation which is currently still subjective.[7]
- Thyroxine levels may be low and thyroid-stimulating hormone (TSH) will also be low.
- Gonadotrophins and sex hormones may be low. In children, growth hormone should be measured.
- Prolactin may be elevated but not as high as in a prolactin-producing tumour.[6]
- Formal perimetry is required for visual fields.

Differential diagnosis
- Adrenal hypoplasia.
- Adrenal insufficiency.
- Congenital adrenal hyperplasia.
- Cerebromeningioma.
- Cushing's syndrome including exogenous glucocorticoid therapy.
- Hypopituitarism.
- Other causes of skin pigmentation - eg, jaundice (also affects the sclerae) and haemochromatosis (more of a bronze colour, may be associated with hepatomegaly and possibly splenomegaly).

Management[1]
Further reading & references

The development of novel medical therapies for this rare but complex and poorly understood condition. Radiotherapy may be the preferred option for an invasive adenoma showing progression. Fractionated external beam radiotherapy or stereotactic radiosurgery can be used depending on tumour size and location. Modern techniques with high-power linear accelerators cause less radiation scatter and so less collateral damage. Radiotherapy is associated with serious long-term problems, including learning and memory difficulties, visual damage and risk of secondary tumours.

Studies assessing stereotactic radiosurgery in the form of gamma knife surgery have been conflicting and its role is not yet clear. Treatment uses focused protons rather than photons (X-rays) and has effected a cure in some patients in whom surgery has been unsuccessful. Panhypopituitarism and cranial nerve palsies are recognised complications.

Medical therapies have generally not been shown to be effective. However, case reports have demonstrated cabergoline (a dopamine receptor antagonist) to induce remission successfully in Nelson’s syndrome with decline of ACTH levels and resolution of the microadenoma or macroadenoma. Further studies are required.

Temozolomide is an alkylating agent used in the treatment of malignant melanoma and primary brain tumours. One study has reported the successful use of temozolomide in Nelson’s syndrome after treatment failure with surgery and gamma knife radiosurgery. There are theoretical reasons why octreotide (a parenterally administered somatostatin analogue), glitazones and sodium valproate may be effective in reducing ACTH secretion but there is no human evidence of their effectiveness.

Prognosis

The prognosis is good, providing there is early recognition. Co-ordination between surgeons and radiotherapists is important. Postoperative aftercare, with adequate long-term monitoring and replacement of hormones, is vital. Blood pressure should also be monitored.

Prevention

- Bilateral adrenalectomy is said to carry an acceptable risk but follow-up should include awareness of Nelson’s syndrome.
- Monitoring of ACTH level and pituitary MRI are recommended 3-6 months after surgery and regularly thereafter.
- Routine pituitary irradiation after bilateral adrenalectomy is no longer recommended due to the risks. However, neoadjuvant radiotherapy may delay and possibly prevent Nelson’s syndrome in those patients with residual pituitary tumour at the time of adrenalectomy, although radiosurgery may become a safer alternative.

The development of computer-assisted 3D MRI volume measurement technology promises more accurate and objective monitoring of patients so that Nelson’s syndrome can be diagnosed as early as possible. Cellular-based in vitro studies, looking at various neuroreceptor functions, are needed to elucidate which subgroup of patients is most likely to develop Nelson’s syndrome, and to aid in the development of novel medical therapies for this rare but complex and poorly understood condition.

Further reading & references
