= Hypopituitarism =

Hypopituitarism is the decreased (hypo) secretion of one or more of the eight hormones normally produced by the pituitary gland at the base of the brain . If there is decreased secretion of most pituitary hormones , the term panhypopituitarism (pan meaning " all ") is used .

The signs and symptoms of hypopituitarism vary , depending on which hormones are undersecreted and on the underlying cause of the abnormality . The diagnosis of hypopituitarism is made by blood tests , but often specific scans and other investigations are needed to find the underlying cause , such as tumors of the pituitary , and the ideal treatment . Most hormones controlled by the secretions of the pituitary can be replaced by tablets or injections . Hypopituitarism is a rare disease , but may be significantly underdiagnosed in people with previous traumatic brain injury . The first description of the condition was made in 1914 by the German physician Dr Morris Simmonds .

= = Signs and symptoms = =

The hormones of the pituitary have different actions in the body , and the symptoms of hypopituitarism therefore depend on which hormone is deficient . The symptoms may be subtle and are often initially attributed to other causes . In most of the cases , three or more hormones are deficient . The most common problem is insufficiency of follicle @-@ stimulating hormone (FSH) and / or luteinizing hormone (LH) leading to sex hormone abnormalities . Growth hormone deficiency is more common in people with an underlying tumor than those with other causes .

Sometimes , there are additional symptoms that arise from the underlying cause ; for instance , if the hypopituitarism is due to a growth hormone @-@ producing tumor , there may be symptoms of acromegaly (enlargement of the hands and feet , coarse facial features) , and if the tumor extends to the optic nerve or optic chiasm , there may be visual field defects . Headaches may also accompany pituitary tumors , as well as pituitary apoplexy (infarction or hemorrhage of a pituitary tumor) and lymphocytic hypophysitis (autoimmune inflammation of the pituitary) . Apoplexy , in addition to sudden headaches and rapidly worsening visual loss , may also be associated with double vision that results from compression of the nerves in the adjacent cavernous sinus that control the eye muscles .

Pituitary failure results in many changes in the skin , hair and nails as a result of the absence of pituitary hormone action on these sites .

= = = Anterior pituitary = = =

Deficiency of all anterior pituitary hormones is more common than individual hormone deficiency .

Deficiency of luteinizing hormone (LH) and follicle @-@ stimulating hormone (FSH) , together referred to as the gonadotropins , leads to different symptoms in men and women . Women experience oligo- or amenorrhea (infrequent / light or absent menstrual periods respectively) and infertility . Men lose facial , scrotal and trunk hair , as well as suffering decreased muscle mass and anemia . Both sexes may experience a decrease in libido and loss of sexual function , and have an increased risk of osteoporosis (bone fragility) . Lack of LH / FSH in children is associated with delayed puberty .

Growth hormone (GH) deficiency leads to a decrease in muscle mass , central obesity (increase in body fat around the waist) and impaired attention and memory . Children experience growth retardation and short stature .

Adrenocorticotropic hormone (ACTH) deficiency leads to adrenal insufficiency , a lack of production of glucocorticoids such as cortisol by the adrenal gland . If the problem is chronic , symptoms consist of fatigue , weight loss , failure to thrive (in children) , delayed puberty (in adolescents) , hypoglycemia (low blood sugar levels) , anemia and hyponatremia (low sodium levels) . If the onset is abrupt , collapse , shock and vomiting may occur . ACTH deficiency is highly similar to primary Addison 's disease , which is cortisol deficiency as the result of direct damage to

the adrenal glands ; the latter form , however , often leads to hyperpigmentation of the skin , which does not occur in ACTH deficiency .

Thyroid @-@ stimulating hormone (TSH) deficiency leads to hypothyroidism (lack of production of thyroxine (T4) and triiodothyronine (T3) in the thyroid) . Typical symptoms are tiredness , intolerance to cold , constipation , weight gain , hair loss and slowed thinking , as well as a slowed heart rate and low blood pressure . In children , hypothyroidism leads to delayed growth and in extreme inborn forms to a syndrome called cretinism .

Prolactin (PRL) plays a role in breastfeeding , and inability to breastfeed may point at abnormally low prolactin levels .

= = = Posterior pituitary = = =

Antidiuretic hormone (ADH) deficiency leads to the syndrome of diabetes insipidus (unrelated to diabetes mellitus) : inability to concentrate the urine , leading to polyuria (production of large amounts of clear urine) that is low in solutes , dehydration and ? in compensation ? extreme thirst and constant need to drink (polydipsia) , as well as hypernatremia (high sodium levels in the blood) . ADH deficiency may be masked if there is ACTH deficiency , with symptoms only appearing when cortisol has been replaced .

Oxytocin (OXT) deficiency generally causes few symptoms , as it is only required at the time of childbirth and breastfeeding .

= = Causes = =

= = Pathophysiology = =

The pituitary gland is located at the base of the brain , and intimately connected with the hypothalamus . It consists of two lobes : the posterior pituitary , which consists of nervous tissue branching out of the hypothalamus , and the anterior pituitary , which consists of hormone @-@ producing epithelium . The posterior pituitary secretes antidiuretic hormone , which regulates osmolarity of the blood , and oxytocin , which causes contractions of the uterus in childbirth and participates in breastfeeding .

The pituitary develops in the third week of embryogenesis from interactions between the diencephalon part of the brain and the nasal cavity . The brain cells secrete FGF @-@ 8 , Wnt5a and BMP @-@ 4 , and the oral cavity BMP @-@ 2 . Together , these cellular signals stimulate a group of cells from the oral cavity to form Rathke 's pouch , which becomes independent of the nasal cavity and develops into the anterior pituitary ; this process includes the suppression of production of a protein called Sonic hedgehog by the cells of Rathke 's pouch . The cells then differentiate further into the various hormone @-@ producing cells of the pituitary . This requires particular transcription factors that induce the expression of particular genes . Some of these transcription factors have been found to be deficient in some forms of rare combined pituitary hormone deficiencies (CPHD) in childhood . These are HESX1 , PROP1 , POU1F1 , LHX3 , LHX4 , TBX19 , SOX2 and SOX3 . Each transcription factor acts in particular groups of cells . Therefore , various genetic mutations are associated with specific hormone deficiencies . For instance , POU1F1 (also known as Pit @-@ 1) mutations cause specific deficiencies in growth hormone , prolactin and TSH . In addition to the pituitary , some of the transcription factors are also required for the development of other organs ; some of these mutations are therefore also associated with specific birth defects .

Most of the hormones in the anterior pituitary are each part of an axis that is regulated by the hypothalamus . The hypothalamus secretes a number of releasing hormones , often according to a circadian rhythm , into blood vessels that supply the anterior pituitary ; most of these are stimulatory (thyrotropin @-@ releasing hormone , corticotropin @-@ releasing hormone , gonadotropin @-@ releasing hormone and growth hormone @-@ releasing hormone) , apart from dopamine , which

suppresses prolactin production . In response to the releasing hormone rate , the anterior pituitary produces its hormones (TSH , ACTH , LH , FSH , GH) which in turn stimulate effector hormone glands in the body , while prolactin (PRL) acts directly on the breast gland . Once the effector glands produce sufficient hormones (thyroxine , cortisol , estradiol or testosterone and IGF @-@ 1) , both the hypothalamus and the pituitary cells sense their abundance and reduce their secretion of stimulating hormones . The hormones of the posterior pituitary are produced in the hypothalamus and are carried by nerve endings to the posterior lobe ; their feedback system is therefore located in the hypothalamus , but damage to the nerve endings would still lead to a deficiency in hormone release .

Unless the pituitary damage is being caused by a tumor that overproduces a particular hormone , it is the lack of pituitary hormones that leads to the symptoms described above , and an excess of a particular hormone would indicate the presence of a tumor . The exception to this rule is prolactin : if a tumor compresses the pituitary stalk , a decreased blood supply means that the lactotrope cells , which produce prolactin , are not receiving dopamine and therefore produce excess prolactin . Hence , mild elevations in prolactin are attributed to stalk compression . Very high prolactin levels , though , point more strongly towards a prolactinoma (prolactin @-@ secreting tumor) .

= = Diagnosis = =

The diagnosis of hypopituitarism is made on blood tests . Two types of blood tests are used to confirm the presence of a hormone deficiency : basal levels , where blood samples are taken ? usually in the morning ? without any form of stimulation , and dynamic tests , where blood tests are taken after the injection of a stimulating substance . Measurement of ACTH and growth hormone usually requires dynamic testing , whereas the other hormones (LH / FSH , prolactin , TSH) can typically be tested with basal levels . There is no adequate direct test for ADH levels , but ADH deficiency can be confirmed indirectly ; oxytocin levels are not routinely measured .

Generally , the finding of a combination of a low pituitary hormone together with a low hormone from the effector gland is indicative of hypopituitarism . Occasionally , the pituitary hormone may be normal but the effector gland hormone decreased ; in this case , the pituitary is not responding appropriately to effector hormone changes , and the combination of findings is still suggestive of hypopituitarism .

= = = Basal tests = = =

Levels of LH / FSH may be suppressed by a raised prolactin level , and are therefore not interpretable unless prolactin is low or normal . In men , the combination of low LH and FSH in combination with a low testosterone confirms LH / FSH deficiency ; a high testosterone would indicate a source elsewhere in the body (such as a testosterone @-@ secreting tumor) . In women , the diagnosis of LH / FSH deficiency depends on whether the woman has been through the menopause . Before the menopause , abnormal menstrual periods together with low estradiol and LH / FSH levels confirm a pituitary problem ; after the menopause (when LH / FSH levels are normally elevated and the ovaries produce less estradiol) , inappropriately low LH / FSH alone is sufficient . Stimulation tests with GnRH are possible , but their use is not encouraged .

For TSH , basal measurements are usually sufficient , as well as measurements of thyroxine to ensure that the pituitary is not simply suppressing TSH production in response to hyperthyroidism (an overactive thyroid gland) . A stimulation test with thyrotropin @-@ releasing hormone (TRH) is not regarded as useful . Prolactin can be measured by basal level , and is required for the interpretation of LH and FSH results in addition to the confirmation of hypopituitarism or diagnosis of a prolactin @-@ secreting tumor .

= = = Stimulation tests = = =

Growth hormone deficiency is almost certain if all other pituitary tests are also abnormal , and

insulin @-@ like growth factor 1 (IGF @-@ 1) levels are decreased . If this is not the case , IGF @-@ 1 levels are poorly predictive of the presence of GH deficiency ; stimulation testing with the insulin tolerance test is then required . This is performed by administering insulin to lower the blood sugar to a level below 2 @.@ 2 mmol / l . Once this occurs , growth hormone levels are measured . If they are low despite the stimulatory effect of the low blood sugars , growth hormone deficiency is confirmed . The test is not without risks , especially in those prone to seizures or are known to have heart disease , and causes the unpleasant symptoms of hypoglycemia . Alternative tests (such as the growth hormone releasing hormone stimulation test) are less useful , although a stimulation test with arginine may be used for diagnosis , especially in situations where an insulin tolerance test is thought to be too dangerous . If GH deficiency is suspected , and all other pituitary hormones are normal , two different stimulation tests are needed for confirmation .

If morning cortisol levels are over 500 nmol / l , ACTH deficiency is unlikely , whereas a level less than 100 is indicative . Levels between 100 @-@ 500 require a stimulation test . This , too , is done with the insulin tolerance test . A cortisol level above 500 after achieving a low blood sugar rules out ACTH deficiency , while lower levels confirm the diagnosis . A similar stimulation test using corticotropin @-@ releasing hormone (CRH) is not sensitive enough for the purposes of the investigation . If the insulin tolerance test yields an abnormal result , a further test measuring the response of the adrenal glands to synthetic ACTH (the ACTH stimulation test) can be performed to confirm the diagnosis . Stimulation testing with metyrapone is an alternative . Some suggest that an ACTH stimulation test is sufficient as first @-@ line investigation , and that an insulin tolerance test is only needed if the ACTH test is equivocal . The insulin tolerance test is discouraged in children . None of the tests for ACTH deficiency are perfect , and further tests after a period of time may be needed if initial results are not conclusive .

Symptoms of diabetes insipidus should prompt a formal fluid deprivation test to assess the body 's response to dehydration , which normally causes concentration of the urine and increasing osmolarity of the blood . If these parameters are unchanged , desmopressin (an ADH analogue) is administered . If the urine then becomes concentrated and the blood osmolarity falls , there is a lack of ADH due to lack of pituitary function (" cranial diabetes insipidus ") . In contrast , there is no change if the kidneys are unresponsive to ADH due to a different problem (" nephrogenic diabetes insipidus ") .

= = = Further investigations = = =

If one of these tests shows a deficiency of hormones produced by the pituitary , magnetic resonance imaging (MRI) scan of the pituitary is the first step in identifying an underlying cause . MRI may show various tumors and may assist in delineating other causes . Tumors smaller than 1 cm are referred to as microadenomas , and larger lesions are called macroadenomas . Computed tomography with radiocontrast may be used if MRI is not available . Formal visual field testing by perimetry is recommended , as this would show evidence of optic nerve compression by a tumor .

Other tests that may assist in the diagnosis of hypopituitarism , especially if no tumor is found on the MRI scan , are ferritin (elevated in hemochromatosis) , angiotensin converting enzyme (ACE) levels (often elevated in sarcoidosis) , and human chorionic gonadotropin (often elevated in tumor of germ cell origin) . If a genetic cause is suspected , genetic testing may be performed .

= = Treatment = =

Treatment of hypopituitarism is threefold : removing the underlying cause , treating the hormone deficiencies , and addressing any other repercussions that arise from the hormone deficiencies .

= = = Underlying cause = = =

Pituitary tumors require treatment when they are causing specific symptoms , such as headaches , visual field defects or excessive hormone secretion . Transsphenoidal surgery (removal of the

tumor by an operation through the nose and the sphenoidal sinuses) may , apart from addressing symptoms related to the tumor , also improve pituitary function , although the gland is sometimes damaged further as a result of the surgery . When the tumor is removed by craniotomy (opening the skull) , recovery is less likely ? but sometimes this is the only suitable way to approach the tumor . After surgery , it may take some time for hormone levels to change significantly . Retesting the pituitary hormone levels is therefore performed 2 to 3 months later .

Prolactinomas may respond to dopamine agonist treatment ? medication that mimics the action of dopamine on the lactrotrope cells , usually bromocriptine or cabergoline . This approach may improve pituitary hormone secretion in more than half the cases , and make supplementary treatment unnecessary .

Other specific underlying causes are treated as normally . For example , hemochromatosis is treated by venesection , the regular removal of a fixed amount of blood . Eventually , this decreases the iron levels in the body and improves the function of the organs in which iron has accumulated .

= = = Hormone replacement = = =

Most pituitary hormones can be replaced indirectly by administering the products of the effector glands : hydrocortisone (cortisol) for adrenal insufficiency , levothyroxine for hypothyroidism , testosterone for male hypogonadism , and estradiol for female hypogonadism (usually with a progestogen to inhibit unwanted effects on the uterus) . Growth hormone is available in synthetic form , but needs to be administered parenterally (by injection) . Antidiuretic hormone can be replaced by desmopressin (DDAVP) tablets or nose spray . Generally , the lowest dose of the replacement medication is used to restore wellbeing and correct the deranged results , as excessive doses would cause side @-@ effects or complications . Those requiring hydrocortisone are usually instructed to increase their dose in physically stressful events such as injury , hospitalization and dental work as these are times when the normal supplementary dose may be inadequate , putting the patient at risk of adrenal crisis .

Long @-@ term follow up by specialists in endocrinology is generally needed for people with known hypopituitarism . Apart from ensuring the right treatment is being used and at the right doses , this also provides an opportunity to deal with new symptoms and to address complications of treatment .

Difficult situations arise in deficiencies of the hypothalamus @-@ pituitary @-@ gonadal axis in people (both men and women) who experience infertility ; infertility in hypopituitarism may be treated with subcutaneous infusions of FSH , human chorionic gonadotropin ? which mimics the action of LH ? and occasionally GnRH .

= = = Complications = = =

Several hormone deficiencies associated with hypopituitarism may lead to secondary diseases . For instance , growth hormone deficiency is associated with obesity , raised cholesterol and the metabolic syndrome , and estradiol deficiency may lead to osteoporosis . While effective treatment of the underlying hormone deficiencies may improve these risks , it is often necessary to treat them directly .

= = Prognosis = =

Several studies have shown that hypopituitarism is associated with an increased risk of cardiovascular disease and some also an increased risk of death of about 50 % to 150 % the normal population . It has been difficult to establish which hormone deficiency is responsible for this risk , as almost all patients studied had growth hormone deficiency . The studies also do not answer the question as to whether the hypopituitarism itself causes the increased mortality , or whether some of the risk is to be attributed to the treatments , some of which (such as sex hormone supplementation) have a recognized adverse effect on cardiovascular risk .

The largest study to date followed over a thousand people for eight years ; it showed an 87 % increased risk of death compared to the normal population . Predictors of higher risk were : female sex , absence of treatment for sex hormone deficiency , younger age at the time of diagnosis , and a diagnosis of craniopharyngioma . Apart from cardiovascular disease , this study also showed an increased risk of death from lung disease .

Quality of life may be significantly reduced , even in those people on optimum medical therapy . Many report both physical and psychological problems . It is likely that the commonly used replacement therapies still do not completely mimic the natural hormone levels in the body . Health costs remain about double those of the normal population .

Hypopituitarism is usually permanent . It requires lifelong treatment with one or more medicines . But you can expect a normal life span .

= = Epidemiology = =

There is only one study that has measured the prevalence (total number of cases in a population) and incidence (annual number of new cases) of hypopituitarism . This study was conducted in Northern Spain and used hospital records in a well @-@ defined population . The study showed that 45 @.@ 5 people out of 100 @,@ 000 had been diagnosed with hypopituitarism , with 4 @.@ 2 new cases per year . 61 % were due to tumors of the pituitary gland , 9 % due to other types of lesions , and 19 % due to other causes ; in 11 % no cause could be identified .

Recent studies have shown that people with a previous traumatic brain injury , spontaneous subarachnoid hemorrhage (a type of stroke) or radiation therapy involving the head have a higher risk of hypopituitarism . After traumatic brain injury , as much as a quarter have persistent pituitary hormone deficiencies . Many of these people may have subtle or non @-@ specific symptoms that are not linked to pituitary problems but attributed to their previous condition . It is therefore possible that many cases of hypopituitarism remain undiagnosed , and that the annual incidence would rise to 31 per 100 @,@ 000 annually if people from these risk groups were to be tested .

= = History = =

The pituitary was known to the ancients , such as Galen , and various theories were proposed about its role in the body , but major clues as to the actual function of the gland were not advanced until the late 19th century , when acromegaly due to pituitary tumors was described . The first known report of hypopituitarism was made by the German physician and pathologist Dr Morris Simmonds . He described the condition on autopsy in a 46 @-@ year @-@ old woman who had suffered severe puerperal fever eleven years earlier , and subsequently suffered amenorrhea , weakness , signs of rapid aging and anemia . The pituitary gland was very small and there were few remnants of both the anterior and the posterior pituitary . The eponym Simmonds ' syndrome is used infrequently for acquired hypopituitarism , especially when cachexia (general ill health and malnutrition) predominates . Most of the classic causes of hypopituitarism were described in the 20th century ; the early 21st century saw the recognition of how common hypopituitarism could be in previous head injury victims .

Until the 1950s , the diagnosis of pituitary disease remained based on clinical features and visual field examination , sometimes aided by pneumoencephalography and X @-@ ray tomography . Nevertheless , the field of pituitary surgery developed during this time . The major breakthrough in diagnosis came with the discovery of the radioimmunoassay by Rosalyn Yalow and Solomon Berson in the late 1950s . This allowed the direct measurement of the hormones of the pituitary , which as a result of their low concentrations in blood had previously been hard to measure . Stimulation tests were developed in the 1960s , and in 1973 the triple bolus test was introduced , a test that combined stimulation testing with insulin , GnRH and TRH . Imaging of the pituitary , and therefore identification of tumors and other structural causes , improved radically with the introduction of computed tomography in the late 1970s and magnetic resonance imaging in the 1980s .