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# Screening for congenital hypothyroidism

Congenital hypothyroidism requires early treatment to prevent mental retardation. Because newborn babies show no definitive signs the diagnosis may be made only after weeks or months.[1] Hulse *et al* in their paper in a recent *BMJ*[2] report that in North London only 40% of cases of congenital hypothyroidism are recognised clinically before 3 months of age. Of 26 cases of congenital hypothyroidism detected in their screening programme, only two were diagnosed before results of the screening test were available. Experience has been similar in Zurich[1] and in North America, where only eight of 277 cases of documented congenital hypothyroidism, from one million infants screened, were suspected clinically before 2 months of age.[3] An early diagnosis therefore clearly necessitates biochemical screening.

The benefits of early treatment of this condition have been well documented by retrospective studies. A recent review[4] showed that 55% of infants treated in the first 6 weeks of life had an IQ of 90 or more, but only 36% of those starting treatment from 7 to 12 weeks of age. Klein *et al*[5] found that 78% of those treated before 3 months of age achieved an IQ above 85. Similar findings have been recorded by Raiti and Newns.[6] Preliminary data from prospective studies suggest normal growth velocities and neuromuscular and psychological development in treated infants.[1 7 8] But without early diagnosis one-third of patients with congenital hypothyroidism require special schooling and a quarter have an IQ less than 70.[2] Existing screening programmes, however, enable treatment to be started before 8 weeks of age and possibly as early as 2 weeks.[1 3]

Screening programmes for congenital hypothyroidism have already been established in North America, some European countries, Japan, and Australia, and are being introduced in several regions of the United Kingdom.[9] The incidence of primary hypothyroidism detected by such programmes is about one in 4400 live births (compared with one in 16 000 for phenylketonuria), most cases resulting from thyroid dysgenesis.[9] This incidence is considerably higher than that based on clinical studies[10 11]—probably because sensitive thyrotrophin (TSH) assays detect children with ectopic or hypoplastic glands who may not present with obvious cretinism and those with transient hypothyroidism.[3 12 13]

Screening can be performed on cord blood serum,[14] capillary serum taken by heel prick on day 5,[15] or a dried blood filter paper spot taken by heel prick at 2-5 days.[16–18] Most programmes use either assay of thyroxine (T4) with a supplemental TSH assay or TSH alone. Cord blood is easy to obtain and does not need such cumbersome radioimmunoassay procedures as the dried blood spot but it calls for special facilities, and the screening cannot readily be combined with screening for other inborn metabolic errors; moreover, up to 12% of all babies screened for T4 need supplementary TSH determinations.[7 14] Dried blood on filter paper has the advantages that it can be transported over a large area and that the screening can be incorporated into established programmes such as phenylketonuria screening.[19] The filter paper, however, needs to be saturated on both sides and careful arrangements have to be made for collection.

Because of the high frequency of false-positive and false-negative results, screening based on T4 measurement alone has been replaced by programmes using T4 assay with supplemental TSH determinations or assay of TSH alone.[16] Admittedly, assay for TSH alone fails to detect both hypothalamic-pituitary disease, a rare condition (one in 100 000 births) that may not result in mental retardation, and congenital absence of thyroxine-binding globulins, where low T4 concentrations coexist with normal thyroid function. The recall rates and the incidence of false-positive results, however, are lower than in programmes that assay both T4 and TSH.[1 16] We should not underestimate the emotional stress caused by such recall. There is also some controversy about the appropriate cut-off point for TSH measurements in programmes using initial T4 screening.[7 20] Although the TSH assay itself is more expensive than the T4 assay, the lower recall rates in a TSH screening programme make it more cost-effective. Hulse *et al*[2] convincingly show the effectiveness of such a programme. The dried blood assay for TSH, however, is technically more difficult than for T4—an important consideration if the screening is to cover a large geographical area. Serum 3,3',5'-triiodothyronine (reverse T3) and thyroglobulin estimations may not detect all hypothyroid infants.[21 22] The serum T3 concentration is usually normal in these infants and not suitable as a basis for diagnosis.[23]

Nearly all false-negative results in existing screening programmes have arisen from human error, and such a programme should handle from 30 000 to 150 000 samples a year.[9] Since the annual birth rate in Britain is 700 000, a national screening programme would need to be based on regional centres. Centralised laboratories with adequate facilities for quality control and data collection for statistical analysis are of the utmost importance.

In North America the cost of screening is estimated as the equivalent of 28-64p per infant[3]; it would be even less if the screening were based on an established phenylketonuria programme. The cost of institutional care or special schooling for those affected is undoubtedly higher than the cost of such programmes[24-6]—quite apart from the enormous emotional costs. In view of the low clinical detection rate and the severity of the untreated condition we cannot justify any further delay in implementing a national screening programme for congenital hypothyroidism.


[1] Illig R. Congenital hypothyroidism. In: Evered D, Hall R, eds. Hypothyroidism and goitre. *Clinics in endocrinology and metabolism.* Vol 8. London: WB Saunders, 1979:49-62.

[2] Hulse JA, Grant DB, Clayton BE, *et al.* Population screening for congenital hypothyroidism. *Br Med J* 1980;**280**:675-8.

[3] Fisher DA, Dussault JH, Foley TP, *et al.* Screening for congenital hypothyroidism: results of screening one million North American infants. *J Pediatr* 1979;**94**:700-5.

[4] Macfaul R, Grant DB. Early detection of congenital hypothyroidism. *Arch Dis Child* 1977;**52**:87-8.

[5] Klein AH, Meltzer S, Kenny FM. Improved prognosis in congenital hypothyroidism treated before age three months. *J Pediatr* 1972;**81**: 912-5.

[6] Raiti S, Newns GH. Cretinism: early diagnosis and its relation to mental prognosis. *Arch Dis Child* 1971;**46**:692-4.

[7] Walfish PG, Ginsberg J, Rosenberg RA, Howard NJ. Results of a regional cord blood screening programme for detecting neonatal hypothyroidism. *Arch Dis Child* 1979;**54**:171-7.

[8] Dussault JH, Glorieux J, Letarte J, Guyda H, Laberge C. Preliminary report on psychological development at age one of treated hypothyroid infants detected by the Quebec screening network for metabolic diseases. *Clinical Research* 1978;**26**:169A.

[9] Fisher DA. Status of neonatal hypothyroid screening: report from the Quebec International Conference on neonatal thyroid screening. *Proceedings of the eighth international thyroid congress, Sydney, Australia* 1980:IA (abst).

[10] De Jonge GA. Congenital hypothyroidism in the Netherlands. *Lancet* 1976;ii:143.

[11] Alm J, Larsson A, Zetterström R. Congenital hypothyroidism in Sweden. *Acta Paediatr Scand* 1978;**67**:1-3.

[12] Delange F, Dodion J, Wolter R, *et al.* Transient hypothyroidism in the newborn infant. *J Pediatr* 1978;**92**:974-6.

[13] LaFranchi SH, Buist NRM, Murphey WH, Larsen PR, Foley TP. Transient neonatal hypothyroidism detected by newborn screening program. *Pediatrics* 1977;**60**:538-41.

[14] Walfish PG. Evaluation of three thyroid-function screening tests for detecting neonatal hypothyroidism. *Lancet* 1976;i:1208-11.

[15] Delange F, Camus M, Winkler M, Dodion J, Ermans A-M. Thyrotrophin determination on day 5 of life as a screening procedure for congenital hypothyroidism. *Arch Dis Child* 1977;**52**:89-96.

[16] Newborn Committee of the European Thyroid Association. Neonatal screening for congenital hypothyroidism in Europe. *Acta Endocrinol* 1979;**90**, suppl 223:5-29.

[17] Dussault JH, Morissette J, Letarte J, Guyda H, Laberge C. Modification of a screening program for neonatal hypothyroidism. *J Pediatr* 1978;**92**: 274-7.

[18] Mitchell ML, Larsen PR, Levy HL, Bennett AJE, Madoff MA. Screening for congenital hypothyroidism. Results in the newborn population of New England. *JAMA* 1978;**239**:2348-51.

[19] Dussault JH, Coulombe P, Laberge C, Letarte J, Guyda H, Khoury K. Preliminary report on a mass screening program for neonatal hypothyroidism. *J Pediatr* 1975;**86**:670-4.

[20] Morissette J, Dussault JH. Commentary: the cut-off point for TSH measurement or recalls in a screening program for congenital hypothyroidism using primary T4 screening. *J Pediatr* 1979;**95**:404-6.

[21] Ginsberg J, Walfish PG, Chopra IJ. Cord blood reverse T3 in normal, premature, euthyroid low T4, and hypothyroid newborns. *J Endocrinol Invest* 1978;**56**:633-42.

[22] Osotimehin B, Black EG, Hoffenberg R. Thyroglobulin concentration in neonatal blood: a possible test for neonatal hypothyroidism. *Br Med J* 1978;ii:1467-8.

[23] Klein AH, Foley TP, Larsen PR, Agustin AV, Hopwood NJ. Neonatal thyroid function in congenital hypothyroidism. *J Pediatr* 1976;**89**: 545-9.

[24] Report of a Committee of the American Thyroid Association. Recommendations for screening programs for congenital hypothyroidism. *J Pediatr* 1976;**89**:692-4.

[25] Report of a Committee of the American Thyroid Association. Recommendations for screening programs for congenital hypothyroidism. *Am J Med* 1976;**61**:932-4.

[26] Report of a Committee of the American Thyroid Association. Recommendations for screening programs for congenital hypothyroidism. *Can Med Assoc J* 1977;**116**:631-2.


# Familial Mediterranean fever

Familial Mediterranean fever is an inherited disease almost exclusively confined to populations originating on the south and east coasts of the Mediterranean Sea. It is rarely seen in Britain and Europe, but doctors in Israel and North Africa are familiar with its features. The syndrome, consisting of irregular episodes of fever with painful serositis and associated with insidiously developing amyloidosis, has been described many times since the turn of the century[1] under the names of benign paroxysmal peritonitis, periodic peritonitis, and maladie periodique as well as familial Mediterranean fever.

Analysis of reported cases shows that families affected by familial Mediterranean fever originate in Morocco, Tunis, Algeria, Libya, Israel, Northern Egypt, and Iraq, though occasional cases are seen elsewhere. Sephardic Jews are quite commonly affected, but Ashkenazic Jews hardly at all. Genetic analysis of several hundred families has shown that the disease closely follows the pattern of autosomal recessive inheritance.[2]

The clinical features of familial Mediterranean fever are not present in the newborn, but may appear as early as the first year of life. Over half of sufferers have had an attack by the age of 10 years, and 80-90% by the age of 20. Attacks of various types occur unpredictably, often once a month or more, with occasional remissions lasting for a few months. Remissions are sometimes associated with pregnancy. The most common type of attack, affecting almost all patients at some time, is abdominal. Pain may begin in any part of the abdomen and spreads rapidly, peritonism, fever, vomiting, and absent bowel sounds developing within a few hours. The pain and fever begin to abate, however, after a few hours and the patient has usually recovered within 48 hours. Laparotomy and appendicectomy are often carried out during a first attack. This misplaced surgery does have the advantage that an acute appendicitis will not be mistaken for an attack later in life.

Attacks affecting the pleura on one or both sides of the chest have a similar course, and a chest radiograph taken during the attack often shows a small, transient pleural effusion. Episodes of pleurisy are not as frequent as abdominal attacks, but synovitis is almost as common. The synovitis may persist for only a day or two, with fever and painful effusion into a large joint. Occasionally the effusion may be chronic, lasting for several months with the development of osteoporosis around the affected joint; but recovery is almost always spontaneous and complete. Sacroiliitis has been reported in young sufferers,[3] but it is not associated with the HLA-B27 tissue type.[4] A characteristic feature of familial Mediterranean fever during attacks of fever or synovitis is a sharply defined erysipelas-like skin lesion. This occurs on the lower leg and may be up to 15 cm in diameter.

No underlying cause for familial Mediterranean fever has so far been discovered, despite extensive searches for infective, metabolic, and toxic agents. Non-specific changes in circulating complement components[5] and in immunological responses[6] have been described, and during acute attacks the erythrocyte sedimentation rate is raised; but no specific diagnostic test is yet available. Effusions may contain polymorphonuclear leucocytes or other phagocytes, and occasionally these cells have small inclusion bodies, thought to be triglyceride. The observation that acute attacks may disappear after haemodialysis is begun[7] supports the possibility of a metabolic cause.