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秦皇岛地区新生儿先天性甲状腺功能低下症的筛查及诊断分析 *

葛 辛[1] 戴向楠[2] 华天书[1] 庞世峰[1] 吴志刚[1△] 卢艳辉[3]

(1 秦皇岛市妇幼保健院遗传优生实验室 河北 秦皇岛 066000;
2 秦皇岛市妇幼保健院小儿遗传代谢病门诊 河北 秦皇岛 066000;3 河北北方学院附属第一医院儿内科 河北 张家口 075061)

摘要 目的:分析秦皇岛地区新生儿先天性甲状腺功能低下症(congenital hypothyroidism,CH)患儿的筛查和诊断结果,为进一步提高新生儿筛查的管理及提高新生儿生命健康质量提供依据和参考。**方法:**回顾性分析秦皇岛地区 2011 年 1 月至 2017 年 1 月共 184308 例新生儿的 CH 筛查资料和诊断结果。统计确诊 CH 患儿的基本情况、体检情况、筛查检验情况、确诊检验情况及治疗随访情况。**结果:**共筛查 184308 例新生儿,其中 92 例为确诊 CH 患儿,发病率 1/2003(0. 499 ‰)。新生儿 CH 临床非特异性表现复杂多样,多表现为病理性黄疸,占 72.8 %,经治疗后黄疸消退时间 17~48 天;其次为前囟大、后囟未闭,占 58.7 %;少哭、喑哑次之,占 51.1 %;其他临床表现为消化道症状(腹胀、肠鸣减弱、便秘、脐疝)、特殊面容、粘液水肿等。CH 患儿筛查检验促甲状腺激素(Thyroid Stimulating Hormone),TSH 重度升高者占 52.2 %,中度升高者为 26.1 %,轻度升高者为 21.7 %。CH 患儿绝大部分表现为 TSH 升高和甲状腺激素 (thyroxine,T4) 降低。经口服左旋甲状腺素钠片治疗 2 周后, 患儿症状改善, 并根据三碘甲状腺氨酸(Triiodothyronine,T3)、T4、TSH 检测结果调整剂量,恢复后每三个月复查一次。36~48 个月随访,患儿身高、体重基本达到正常参照标准。**结论:**秦皇岛地区新生儿 CH 发病率较全国水平(1/3120)稍高,需加强 CH 患儿非特异性临床表现的健康教育工作,通过新生儿 CH 筛查做到早发现、早诊断、早治疗,提高新生儿的生命健康。

关键词:先天性甲状腺功能低下症;新生儿;筛查;黄疸
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Screening and Diagnosis of Congenital Hypothyroidism in Neonates of Qinhuangdao Area*

GE Xin[1], DAI Xiang-nan[2], HUA Tian-shu[1], PANG Shi-feng[1], WU Zhi-gang[1△], LU Yan-hui[3]

(1 Laboratory of Ecology and Eugenics, Maternal and Child Health Hospital of Qinhuangdao City, Qinhuangdao, Hebei, 066000, China; 2 Pediatric genetic metabolic disease outpatient clinic, Maternal and Child Health Hospital of Qinhuangdao City, Qinhuangdao, Hebei, 066000, China; 3 Pediatric Internal Medicine Department, The First Affiliated Hospital of Hebei North University, Zhangjiakou, Hebei, 075061, China)

ABSTRACT Objective: To analyze the results of screening and diagnosis of neonatal congenital hypothyroidism (CH) in Qinhuangdao, and provide references to improve the management of screening and the quality of life and health for newborns. **Methods:** The CH screening data and diagnosis results of a total of 184308 newborns were retrospectively analyzed from Jan 2016 to Jan 2017 in Qinhuangdao. The basic situation, physical examination, screening test, confirmed diagnosis and treatment follow-up situation of Diagnosed CH children were counted. **Results:** A total of 184308 newborns were screened, of which 92 were diagnosed as CH, and the incidence rate was 1/2003 (0.499 ‰). The clinical non-specific symptoms of newborn CH were complex and diverse, pathological jaundice was the main symptom, accounting for 72.8 %, after 17 to 48 days, jaundice subsided; followed by the symptoms of former fontanel, after fontanelle not closed, accounting for 58.7 %; the symptoms of less cry, dumb, accounting for 51.1 %; other clinical symptoms were gastrointestinal symptoms (abdominal distension, bowel weaken, constipation, umbilical hernia), special face, mucus edema, et al. CH newborns were significantly high in thyrotropin, thyroid stimulating hormone (TSH), 26.1 % in moderate and 21.7 % in mild. Most CH newborns showed elevated TSH and decreased thyroid hormone (triiodothyronine, T4). After oral administration of L-thyroxine sodium tablets for 2 weeks, the children's Symptoms were improved. According to Triiodothyronine (T3), T4, TSH test results, the dose should be adjusted. After recovery, the children reviewed every three months, 36 to 48 months follow-up, the height and weight of children basically reached the normal reference standard. **Conclusions:** The incidence of CH in neonates of Qinhuangdao area was slightly higher than that of the national level (1/3120), and it was necessary to strengthen the health education work of non-specific

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作者简介:葛辛(1980-),女,本科,主管检验师,研究方向:秦皇岛地区多种新生儿疾病筛查及网络化管理对于降低出生人口缺陷的研究,E-mail: gexin_1980@medicinepap.cn

△ 通讯作者:吴志刚(1966-),男,主管检验师,研究方向:秦皇岛地区多种新生儿疾病筛查及网络化管理对于降低出生人口缺陷的研究,E-mail: wuzhigang_1966@medicinepap.cn

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clinical manifestations of CH newborns. The neonatal CH screening could be used for early detection and early diagnosis to improve the quality of life and health of newborns.

Key words: Congenital Hypothyroidism; Newborns; Screening; Jaundice

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前言

CH 又称作先天性甲低，是幼儿时期常见的智残性疾病，也是一种常见的新生儿内分泌疾病，主要是由患儿甲状腺先天性缺陷或因母孕期饮食中缺碘所致[1]。CH 早期没有明显表现，症状一旦出现，是不可逆的，故也叫呆小病[2]。医学上一般认为若是 2 个月内发现，通过及时治疗、终身服药，儿童智力基本可以正常，若大于 10 个月发现，即使治疗，智商也只能达到正常的 80 %，若大于 2 岁才发现，则智力落后不可逆。CH 的发病率大约是五千分之一[3]，临床表现为智力迟钝、生长发育迟缓及基础代谢低下，临床上几乎所有未及时发现并治疗的患儿均表现为体格和智力发育障碍[4,5]。为降低新生儿发病率、避免新生儿神经精神发育严重缺陷、减轻家庭和国家负担，我国于 1995 年颁布了《母婴保健法》，明确规定将 CH 列入新生儿筛查疾病[6-8]。早期的干预有助于帮助患儿进行体格和智力发育异常的纠正。本研究回顾性分析秦皇岛地区 2011 年 1 月至 2017 年 1 月共 184308 例新生儿的 CH 筛查资料和诊断结果，旨在为进一步提高新生儿筛查的管理和提高新生儿生命健康质量提供依据和参考。

1 资料与方法

1.1 一般资料

秦皇岛地区各医院产科从 2011 年 1 月至 2017 年 1 月出生的新生儿，共 184308 例。新生儿出生 72 h 后，充分哺乳 2-7 d，采足跟血，制备干血滤纸片标本，由筛查中心检测。

1.2 筛查方法及标准

对出生 72 h、充分哺乳 2-7 d 的新生儿采足跟血，将足跟血滴于滤纸上(美国产 SS&903 型滤纸)，共需采集 3 个血斑，保证每个血斑直径大于 8 mm，采集血斑时要保证血斑渗透到滤纸的背面，让血滴自然渗透、干燥后，装入塑封袋中于 4℃保存，并集中送检。筛查中心以 DELFIA-1420 型分析仪及相应配套试剂盒检测干血滴纸片中 TSH 含量。根据试剂盒上的指标，足跟 TSH 正常值为 9 μIU/mL，<9 则为阴性，≥ 9 为可疑阳性或阳性[1]。新生儿足跟血检测值≥ 9(可疑阳性或阳性)则需要召回新生儿，采集其静脉血，对新生儿的血清游离甲状腺素(free thyroxine，FT4)和足跟 TSH 进行检查。

1.3 确诊方法及标准

以 Access 微粒发光免疫分析仪及相应配套试剂采用化学分析法对 CH 进行确诊检验，测定静脉血 TSH、总甲状腺素(Total thyroid hormone，TT4)、游离甲状腺素(FT4)、总三碘甲状腺原氨酸(Total triiodothyronine, TT3)、游离三碘甲状腺原氨酸(Free triiodothyronine, FT3)。根据《先天性甲状腺功能减低症诊疗共识》，诊断标准为：TSH 升高、甲状腺激素(T4)降低。其中 FT4 的正常值为 9-25 pmol/L，TSH 增高，FT4 降低，则可确诊新生儿患有新生儿先天性甲状腺功能减低症[9,10]。

1.4 统计学分析

采用 SPSS 16.0 进行统计学分析，计量资料以 表示，多组间比较采用单因素方差分析，两组间比较采用 t 检验，计数资料以%表示，组间比较采用卡方检验，以 P＜0.05 为差异有统计学意义。

2 结果

2.1 CH 患儿的基本情况

筛查的 184308 例新生儿中，确诊 CH 患儿共 92 例，发病率为 0.499 ‰。患儿年龄为 14-51 d，平均年龄(24.7± 2.9) d，男孩占 52.2 % (48 例)，女孩占 47.8 % (44 例)；出生体重：2250-g 5 例，其中 3 例为早产儿，另 2 例为足月小样儿，2500-g 84 例，4000-4300 g 3 例；胎龄分布：35-37 周 3 例，38-42 周 85 例，＞42 周 4 例。

2.2 CH 患儿的体检情况

新生儿 CH 的临床非特异性表现复杂多样，多表现为病理性黄疸，共 67 例(占 72.8 %)，其中生理性黄疸消退延迟 28 例(26 例足月儿，1 例过期产儿，1 例早产儿)，重度黄疸 39 例(37 例足月儿和 2 例早产儿)，经治疗后黄疸消退时间 17-48 天。其次为前囟大、后囟未闭，共 54 例，占 58.7 %。少哭、喑哑次之，共 47 例，占 51.1 %。其他还有消化道症状，如腹胀、肠鸣减弱、便秘、脐疝等。另还有特殊面容、粘液水肿等情况。患儿的非特异临床表现情况如下，见表 1。

2.3 CH 患儿的筛查检查结果

确诊 CH 患儿的 TSH 筛查结果：TSH 重度升高 (≥ 32 m IU/ml)的患儿有 48 例，占 52.2 %；TSH 中度升高(≥ 32 m IU/mL)的患儿有 24 例，占 26.1 %；TSH 轻度升高(≥ 32 m IU/mL)的患儿有 20 例，占 21.7 %。见表 2。

2.4 CH 患儿的确诊检查结果

CH 患儿的确诊检查 (FT3、FT4、TT3、TT4、TSH 化验检查)结果：所有的结果均表现为 TSH 升高，T4 降低。即可确诊为 CH。具体情况见表 3。

2.5 CH 患儿的治疗、随访

新生儿 CH 确诊后立即口服左旋甲状腺素钠片，剂量 8~10 μg/kg，1 次 /d，在治疗过程中，要注意观察孩子的精神状况。治疗开始之后，应定期复查血中甲状腺激素及 TSH，开始每周查一次。服药 2 周，患儿便可出现食欲增加、便秘减退、语言和活动增多等症状改善现象，并根据静脉血 T3、T4、TSH 检测结果调整用药剂量，维持患儿 FT4、TSH 在正常范围内，每三个月进行一次复查及体格、智力发育检查。36~48 个月随访显示患儿身高(97.6± 3.8) cm、体重(14.7± 3.3) kg 基本达到正常标准。患儿病情稳定后，每半年至一年复查一次，并检查腕骨 X 线片，明确骨龄的发育情况。

表 1 CH 患儿的临床表现

Table 1 Clinical manifestations of CH children

Clinical manifestation	Case	Percentage(%)
Pathologic jaundice	67	72.8
The anterior fontanelle, posterior fontanelle arteriosus	54	58.7
Cry less, speak hoarse	47	51.1
Bowel distension / weaken	42	45.7
Feeding difficulties	36	39.1
Sleepiness	35	38.0
Low heart sounds and slow heart rate	18	19.6
constipation	17	18.5
Cranial suture open	10	10.9
Umbilical hernia	10	10.1
Special face	7	7.6
Rough skin	3	3.3
Mucous edema	2	2.2

表 2 CH 患儿的 TSH 水平分布

Table 2 The distribution of TSH level of CH children

TSH level	Case	Percentage(%)
TSH slightly elevation(10~15 m IU/mL)	20	21.7
TSH moderately elevation(15~32 m IU/mL)	24	26.1
TSH severe elevation(≥ 32 m IU/mL)	48	52.2

表 3 CH 患儿的确诊检查结果

Table 3 The confirmed results of diagnosis of CH children

TSH level	Case	Percentage(%)
TSH increased, TT3, TT4 and FT3, FT4 decreased	24	26.1
TSH increased, only TT4 and FT4 decreased	50	54.3
TSH increased and only FT4 decreased	10	10.9
TSH increased and only TT4 decreased	8	8.7

3 讨论

通过新生儿筛查可以避免新生儿重要脏器的不可逆损害、避免生长发育和智力发育迟缓或落后，提高人口素质，从而减轻家庭和社会负担，提高新生儿的生命健康质量[11,12]。我国新生儿全面筛查始于 1985 年，根据卫生部规定，医生在正常出生的新生儿出生 72 小时后，早产儿出生 7 天后，就要采血送往筛查中心检查 [13,14]。研究结果显示秦皇岛地区的新生儿筛查率达 88.2 %，高于全国平均水平(近 60 %)；同时，秦皇岛地区的新生儿 CH 发病率为 1/2003(0. 499 ‰)，也高于 2004 年的全国平均水平 1/3120(0. 332 ‰)。我国 CH 发病率总体呈现上升趋势，特别是 1998 年至 2006 年，发病率明显升高，这和新生儿筛查率和筛查手段的提高有着明显关系[15,16]。同时，不同地区的 CH 发病率有所不同，这可能与当地的生活习俗、卫生条件、筛查条件等因素有关[17,18]。

CH 分为两种，一种是由于患儿甲状腺先天性缺陷所致，称散发性甲状腺功能减低症；一种是因母孕期饮食中缺碘所致，称地方性甲状腺功能减低症[19,20]。当患儿的甲状腺不发育或者发育不全导致功能不足时，即可引起生长发育迟缓和智力发育障碍等，还有代谢障碍和生理功能低下，海马功能异常等，由此可导致一系列的临床症状[21-24]，如头围大、囟门及颅缝明显增宽，喂养困难、腹胀、肠鸣减弱、顽固性便秘、极易发生呕吐和呛咳等消化系统症状，同时可能出现嗜睡、哭声嘶哑、生理性黄疸期延长、体重不增或增长缓慢，可有暂时性低体温[25]。患儿特殊面容包括额头部位皱纹多、脸部臃肿、鼻根平、眼距宽、且眼睑厚、发际低等[26]。在本研究中，临床表现以病理性黄疸最为多见，占 72.8 %。先天性甲状腺功能低下主要是由甲状腺发育不全导致的，可能涉及四个方面：机体内存在对甲状腺细胞生长有抑制作用的免疫蛋白；甲状腺合成中的关键酶缺失；促甲状腺激素缺失；相关靶器官或靶细胞反应低下[27]。

目前 CH 筛查方法主要为检测血液 TSH 浓度[28]。T4 是诊断 CH 的敏感指标，甲状腺功能减低会伴随着血清中 T4 的降低，TSH 联合 T4 检查是确诊 CH 的理想方法[29]。但由于该方法造价较高，目前国内仅对新生儿进行 TSH 筛查，作为一种敏感度和特异度都较高的筛查方法，这种方法在国内被广泛应用，并且筛查方法简便，检出率高[30]。该方法同时也存在不足之处：仅对甲状腺缺损、发育不良等引起的原发性 CH 有较高的准确度，而某些中枢性甲状腺功能减低症患儿血 TSH 不升高，因此无法准确检查。同时，部分 CH 患儿存在 TSH 延迟升高的现象，在一般采血时间患儿 TSH 未升高，因此也无法准确检测。所以，新生儿 CH 的发病率可能还会比检测出来的发病率还要高，我们需警惕漏诊病例的发生。而一旦发生，这一部分未能通过检测血液 TSH 浓度的患儿将会因为得不到及时的诊断和治疗，而发生体格和智力发育障碍，影响新生儿生命健康质量。

CH 的预后与开始治疗的年龄密切相关。最关键的是早期确诊，及时治疗，以减小对脑发育的损害。在出生后三个月接受治疗者，智商 90 分以上者有 75 %；出生后四到六个月接受治疗者，智商 90 分以上者仅占 33 %，有不可逆脑损伤后遗症者达 15 %。同时，孩子生长发育迅速，在治疗过程中及时补充钙、铁、维生素等微量元素和维生素至关重要，饮食中也应富含蛋白质和矿物质等。如果患儿的 CH 是由家族性酶缺陷引起的，还应该注意补碘[16]。同时，患儿需要终身服用甲状腺制剂。

我国的新生儿筛查工作虽然始于上世纪八十年代，但是仍然存在着很多的不足，这些不足给新生儿的筛查和后续治疗工作带来了极大的困扰。主要如下：(1)新生儿筛查工作发展不平衡。上海、北京、浙江等地的筛查率达到了 95 %以上，其他很多省份参差不齐，例如安徽省 2010 年筛查率只有 57 %，除此之外还有筛查量、筛查技术等方面的差异。(2)部分省市新生儿筛查工作的网络还未形成。(3)新生儿筛查的信息化管理程度低，目前还有 50 %以上的省未建立筛查数据库信息管理系统。(4)全国筛查机构存在重筛查、轻随访的问题。随访是确保预后良好的一个重要保障，一旦被忽视，就失去了筛查的意义。(5)缺乏治疗规范和指南，不同地区的筛查缺乏统一的确诊和治疗标准，很多省市的筛查机构甚至没有质量评估。总体而言，我国的新生儿筛查虽然仍然存在着极大地弊端和不足，新生儿筛查 CH 的道路还很漫长。

综上所述，秦皇岛地区新生儿 CH 发病率较全国水平(1/3120)稍高，需加强 CH 患儿非特异性临床表现的健康教育工作，通过新生儿 CH 筛查做到早发现、早诊断、早治疗，提高新生儿的生命健康质量。

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(上接第 720 页)

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