Neonatal Screening Program - Establishment, Evaluation, and Follow-up Survey -

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1. Significance of neonatal screening and its background

1) Significance of screening

In the conventional system of healthcare policy, screening was planned and implemented, but the next plan was prepared without evaluating the results. On the other hand, the system of the current healthcare policy is to improve the quality continuously, applying the PDCA cycle of plan, do, check, and act for improvement, and then the next plan.

Since the major objective of the healthcare policy is "disease control," the following 5 conditions are set to select target diseases for screening as secondary prevention. These conditions have emerged through the history of neonatal screening.

2) Background of the screening

Congenital hypothyroidism (hereinafter referred to as "CH"), which is now the most appropriate target disease of screening in the world, used to be a disease that in most cases could not be detected before the onset of severe clinical symptoms, thus losing the opportunity of early treatment, before the start of screening, resulting in various degrees of intellectual impairment. For efficient screening, it is necessary to specify the proper cutoff values of the measurement items, to minimize false-negative and false-positive cases as far as possible. Initially CH screening was conducted by sampling blood around 5 days after birth when the TSH and T4 after birth show stable values, and definite cutoff values were used.

Based on the thyroid function in CH cases that were clinically detected before the start of screening, it was considered that the TSH value of the pediatric patient would show an "abnormally high value," and it was recommended in Japan that cases showing a TSH value of 50 mIU/L or higher by blood sampling on filter paper should undergo detailed tests immediately and cases showing 20 to 50 mIU/L should undergo a second blood sampling (re-blood sampling) and undergo detailed tests if a high TSH value still continued.

At the actual screening, however, different results than this assumption occurred one after another. The most unexpected was that the thyroid function in pediatric patients with primary hypothyroidism varied greatly, not only showing overt hypothyroidism with an abnormally high TSH value and low T4 value, but also mild to latent hypothyroidism with a high TSH value and normal to low normal T4 value.

2. What we learned from the screening for congenital hypothyroidism

We could learn various things from the actual screening results, including the above.

1) Change in the reference value (cutoff value) for TSH

In the distribution of TSH values in the false-positive and true-positive cases on actual CH screening, there was considerable overlap, unlike the theoretical assumption, and it was impossible to perform screening efficiently by a single cutoff value. Thus, the cutoff value at which moderate to severe cases of hypothyroidism are subject to immediate detailed tests was changed to around 30 mIU/L, and the system of re-blood sampling was employed if the value was between 10 and 30 mIU/L.

As a result, the frequency of detection of CH in Europe has become 23.8 to 45.4 per

100,000 births (1:2,203) after the start of screening compared to 14.5 to 16.4 before screening. In Japan too the frequency of detection estimated by using the Capture-recapture method (CRM) is 1:2,206.

2) Discovery of new clinical states

(1) Transient hypothyroidism

After the start of screening, various clinical states showing transient hypothyroidism only during the neonatal period have been discovered, and it became well known that cases showing high TSH values for filter paper blood are not limited to permanent hypothyroidism. The major ones include excessive iodine, drugs taken by the mother (such as antithyroid agents), and low-birth-weight babies. Down syndrome is also known to show a specific course.

(2) Mild cretinism, latent hypothyroidism (subclinical hypothyroidism)

Though neonates showing mild to latent hypothyroidism with a high TSH value and normal to low normal value of T4 were not considered before the start of screening, many cases have been detected after screening according to reports from the U.S. and Europe.

3) Handling of premature babies

It has been reported that low-birth-weight babies (premature babies) are not only a cause of transient hyperthyroidism, but also show no increases in TSH values, even in the case of primary hypothyroidism, at the time of routine blood sampling around 5 days after birth. Therefore, in Japan, re-blood sampling by 4 weeks after birth has been recommended after 1987 in addition to the routine blood sampling

According to actual data in Hokkaido, cases of CH and transient hyperthyroidism are approximately 5 and 30 times, respectively, compared to those in mature infants.

4) Disinfectant-containing iodine

In 1982, Gruters, then West Germany, published an article reporting that the disinfectant-containing iodine used for mothers or neonates during the perinatal period could accumulate in the neonate’s thyroid and cause a defect in thyroid hormone synthesis by the Wolff-Chaikoff effect.

In Japan, similar contamination by iodine was verified by measurement of urinary iodine levels, etc., and it was recommended to obstetrical medical institutions to change the disinfectant. The results showed a decrease in the group of 10 to 15 mIU/L of TSH on the filter paper, namely, 0.956 to 0.564%, and a decrease by half in moderately increased cases of 15 to 30 mIU/L, namely, 0.278 to 0.103%. Such increases in iatrogenic false-positive cases should be reduced as far as possible, because they will cause various problems.

5) False-negative cases not detected by screening

After the start of screening, it became known that there are cases that have not been detected or were difficult to detect by TSH screening, not because of errors in the screening process, but the specific clinical state of primary hyperthyroidism.

In the tabulation of the years from 1992 to 2000 in Japan, 35 false-negative cases were reported among screening of about 10 million persons.

3. Evaluation, improvement, and follow-up survey of neonatal screening

The requirements for conducting mass screening for congenital hypothyroidism over a long period depend on evaluation of the following and improvement of any problems:

1) whether the early discovery and early treatment (intervention) as secondary prevention

are properly performed,

2) whether the cost/benefit ratio is good (or, whether any harmful effects are low).

For this purpose, 1) a follow-up system for positive cases, 2) a system to recognize false-negative cases, and 3) a survey of the causes of false-positive cases and preventive measures are necessary.

Accuracy of the screening overall can only be assured by the surveillance loop (monitoring system) of the accumulation/registration of such screening data, data analyses, recommendation of improvements by providing information, activity to improve the quality, change in the screening system, and data accumulation/registration again.

The post-screening survey in Japan was performed by the group of the Ministry of Health and Welfare until about 1987 as an annual national survey, and one institution was responsible for the survey after 1994.

A follow-up survey is essential because the follow-up survey has shown that a considerable number of diagnoses by the physician in charge of detailed tests (general pediatrician) were changed by the physician specialized in pediatric endocrine secretion.

In addition, there is another problem concerning the qualifications of screening laboratories.

In Japan, local governments have the responsibility to perform screening. For economical reasons (cheaper tests) due to the current financial situation, the screening laboratories have easily been changed, causing problems in accuracy management and assurance.

For screening, the judgment should be made by only one test, because blood is sampled from a population of neonates, many of whom are thought to be normal neonates without symptoms. Thus, accuracy is required during the complete process from blood sampling to measurement, judgment, and notification of the result; and nearly zero false-negative results can only be assured by accuracy management and assurance that the system works properly.

For accuracy assurance of the complete screening in Japan, a “central surveillance organization” is necessary.

No institutions have played such a role so far. Under these circumstances, the National Center for Child Health and Development was established in March 2002, and its major role is to “develop a healthy next generation” in a “society with an extremely decreasing birthrate.” For this purpose, it is necessary to accumulate evidence that will be the basis for recommending policies, promoting children’s health and development, and promoting research, and it is expected that the National Center for Child Health and Development will play an important role in the follow-up survey of neonatal screening, evaluation of the screening based on the results of the follow-up survey, and improvement.