An Audit of biotinidase screening at a tertiary children's hospital before and after implementation of an evidence-based practice guideline for developmental delay

Michael O Ogundele

Author details:
Michael O Ogundele
Department of Community Paediatrics,
Alder Hey Royal Children's Foundation Hospital
NHS Trust, Liverpool, L12 2AP

Address for Correspondence:
Dr M O Ogundele,
40 Redruth Road,
Liverpool, L11 6NA, UK.
Tel: 00447742199280
E-mail: m.ogundele@nhs.net

Abstract

Aim:

An evidence-based protocol for investigation of children with global developmental delay was introduced in 2010, recommending that biotinidase activities (BTA) should be measured early in the clinical pathway for moderate to severe delay. We aimed to compare the rate and results of screening for biotinidase deficiency (BTD) before and after the introduction of the guideline.

Method:

We retrospectively analysed the laboratory data for all patients tested for BTD in a large tertiary children's hospital over a period of 2 years before and 2 years after the guideline implementation.

Results:

150 tests of BTA were requested in 138 patients aged 1 month to 17 years 7months (median 2 years 3 months). A total of 10 (6.7%) abnormal results were found and 8 patients were diagnosed with partial BTD, corresponding to an annual incidence of 0.357 (0.18 to 0.54) per 1000 live births. The monthly rate of BTA tests requested progressively increased from 0.31 in 2008 to 1.11 per 1000 live births in 2011, but the annual rate of positive diagnosis decreased from an average of 10% before the introduction of the guidelines to 4.5% in 2010-2011 after its implementation.

The commonest symptoms of patients diagnosed with partial BTD were either neuro-developmental delay (87.5%) or neurological abnormalities (75%), and included complex epilepsy or seizure disorders (62.5%), learning difficulties (37.5%) and hearing loss (25%).

Conclusion:

This study suggests that the prevalence of BTD in a cohort of selected patients in a tertiary hospital with developmental delay or other neurological disorders is about 60 times higher than the estimated incidence of 0.008 (0.006 to 0.009) per 1000 live births in the developed countries. The lower rate of positive results after the guideline implementation (10% vs 4.5%) suggests that the investigations were being ordered simply as pathway-led procedure rather than based on strong clinical suspicion.

Keywords:
Biotinidase deficiency; Biotinidase Screening; Biotin; Global developmental delay; Audit; Practice Guideline

Introduction

Biotinidase deficiency (BTD) is an autosomal recessively inherited metabolic disorder that manifests during childhood with various cutaneous and neurological symptoms particularly seizures, hypotonia, developmental delay, ataxia, dermatitis, hair loss, mental retardation, lactic acidosis, hearing and visual loss, organic aciduria and foetal malformations (Wolf, 1991). BTD is also known to present as cerebral palsy (Livne 1994), and other developmental disorders such as autism (Manzi et al, 2008).

Biotin is a water-soluble vitamin that is used as a co-factor by enzymes involved in carboxylation reactions in mammals. Dietary biotin exists in free and protein-bound forms (Said et al, 1993). Biotinidase (BT) is secreted either in pancreatic fluids or derived from the intestinal flora, intestinal secretions and brush-border membranes. It plays a critical role in releasing free biotin from dietary biotin (biocytin and biotinylated peptides) prior to absorption (Wolf, 1991; Zempleni et al, 2008).

BTD is easily treated with biotin supplementation with reversal of most symptoms if commenced early (Grunewald et al, 2004). Treatment typically consists of lifelong daily doses of biotin 5–20 mg to compensate for decreased bioavailability from food sources and increased urinary losses (Wolf, 1991). There are reported symptomatic cases of BTD diagnosed after neonatal period which did not respond to biotin treatment. Such cases include autism (Zaffanello et al, 2003), hearing impairments, optic atrophy, developmental delay (Hoffman et al, 2005) and persistent spastic paraparesis (Chedrawi et al, 2008). On the other hand, some patients with BTD having residual BT activities >1% have been reported, who remain asymptomatic even without treatment (Möslinger et al, 2001).

BTD is one of the inborn metabolic diseases amenable to simple neonatal or postnatal screening. Newborn screening may be cost effective because delay in diagnosis results in irreversible morbidity, while early therapy prevents most of the neurological sequelae (Vallejo-Torres et al, 2015).

There have conflicting recommendations and different practices with regard to inclusion of BTD within the neonatal screening programmes in various developing and advanced countries worldwide (Wolf, 2015). The latest advice from the UK National Screening Committee with regard to BT newborn screening is that "A systematic population screening programme is not recommended" (NSC, 2013, available online on https://legacyscreening.phe.org.uk/biotidinasedeficiency).

Learning disability (LD)/Global Developmental Delay (GDD) is a common problem affecting 1-3% of the population. Moderate mental retardation is a recognized manifestation of cerebral dysfunction in patients with profound BTD. Given the low yield of about 1%, conflicting recommendations have been given for the role of routine metabolic screening for inborn errors of metabolism, including BTD, in the evaluation of children with GDD or LD. Some authors have promoted the need for universal newborn screening of BT activity, rather than clinical-based screening (Shevell et al, 2003). A pre-selection of cases using a stepwise or checklist approach (including the presence of dysmorphologic symptoms, hepato-splenomegaly, and ophthalmologic and neurologic findings etc), which could increase the yield to 13.6% have also been advocated (van Karnebeek et al, 2005).

Some evidence-based clinical guidelines have recommended that Biotinidase Activities (BTA) should be measured early in the investigation pathway for Global Developmental Delay (McDonald et al, 2006). An evidence-based protocol was introduced in 2010 at the local tertiary

children's hospital for investigation of children with moderate to severe Global Developmental Delay (GDD).

1. Methods and Design

We retrospectively analysed laboratory record of all patients who were tested for biotinidase deficiency in a large tertiary children's hospital over a four-year period. The laboratory record was obtained from the Hospital Computer system. The data collected for each patient included age at testing, the requesting doctor, outcome of the test, and the final diagnosis. The audit was completed as part of the Clinical Governance strategies of the Royal Alder Hey Children's Hospital. No identifiable patient record was used and no research ethical approval was required. Further clinical management and treatment of the affected patients has not been reported in this study.

Biotinidase level was estimated using spectrophotometric techniques. Normal reference levels of biotinidase activities (BTA) used to classify the status of BTD of each patient was 3.9-8.9 nmol/ml/min (2.4-8.2 in infants less than 3months). Profound BTD was defined as BTA less than 10% of mean normal serum enzyme activity or < 0.3 nmol/ml/min, and partial BTD was defined as BTA between 10% and 30% of mean normal serum enzyme activity.

Liverpool is a major city and metropolitan borough in North West England, with an estimated population of 478,580 and annual live birth of 5,995 in 2015. The Liverpool city and its surrounding areas form the fifth largest metropolitan area in the UK, with an estimated population of over 2.24 million in 2011.

2. Results

150 tests of BT activities were requested in 138 patients aged 1 month to 17 years 7months (average of 3 years 5 months, and median of 2 years 3 months). The rate of BTA tests requested (monthly per 1000 live births) progressively increased more than three-fold from 0.31 in 2008 to 1.11 in 2011 (Table 1). However the rate of positive diagnosis correspondingly decreased from an average of 10% in 2008 /2009 before the introduction of the LD/GDD guidelines to 4.5% in 2010/2011 after its implementation. A total of 10 (6.7%) abnormal results over the four-year period were found. The BT activities were normal on repeat testing of two patients.

Eight patients were diagnosed with partial BTD corresponding to an annual incidence of 0.477 (0.18 to 0.54) per 1000 live births. This is about 60 times higher than the estimated incidence of 0.008 (0.006 to 0.009) per 1000 for partial BTD in the developed countries (Wolf, 1991). It is almost three times higher than the incidence of combined partial and profound BTD of 0.17 (0.014 to 0.02) per 1000. The age at diagnosis was between 15 months and 17 years 7 months (mean of 7 years, and median of 5 years).

The commonest presentations of patients diagnosed with partial BTD were either developmental delay /neurobehavioral (87.5%) or neurological abnormalities (75%) (Table 2). The commonest individual symptoms were developmental delay (62.5%), complex epilepsy or seizure disorders (62.5%), learning difficulties (37.5%) and hearing loss (25%). Others were hypotonia, challenging behaviour, autistic spectrum disorder, short stature and dysmorphism. One of the patients was diagnosed during admission on the intensive care unit (ICU) following a sudden cardiac arrest from unexplained cardiomyopathy at the age of 13 years.

The patients were referred most often by the Neurologists (50%), Community (or Developmental) Paediatricians (25%) and General Paediatricians (12.5%). 50% of the patients were tested on the request of

Consultants and the rest from other grades of doctors.

3. Discussion

A total of 10/150 (6.7%) abnormal results over the four- year period were found. This study suggests that the prevalence of BTD in a cohort of selected patients in a tertiary hospital with Global Developmental Delay (GDD) or other neurological disorders is higher than in the general population. The BTA were normal on repeat testing of two (20%) patients. This might represent the phenomenon of transient BTD, which has been found to be common in newborn screening of preterm babies (Lawler et al 1992). However the two patients had abnormal results when first tested at the ages of 2 and 8 years respectively. Incidentally, the younger patient was born prematurely at 32 weeks gestational age and later presented with GDD. The older patient presented with a complex range of neurological symptoms including ataxia-dystonia and asymmetrical chorea. The tests became normal after repeating them within 2 to 5 months.

The rate of tests requested (monthly per 1000 live births) increased by more than 100% within one year of introducing an evidence-based guideline which recommended screening for BTD early in the investigation of moderate or severe developmental delay. The lower rate of positive results after the guideline implementation (10% vs 4.5%) suggests that the investigations were being ordered simply as a pathway-led procedure rather than based on strong clinical suspicion of a diagnosis.

Two similar retrospective studies from tertiary level hospitals in India and Iran have recently been published. A cohort of ten children with a median age of 6 months (2 to 46 months) with BTD were reported from a Genetic centre in India (Singh et al., 2015) while Karimzadeh et al (2013) reported a cohort of 16 children aged between 1.5 months and 52 months from Iran, all being offspring of consanguineous marriages.

Screening children with LD /GDD for BTD has previously yielded mixed results. A study of 274 children over a four-year period in the USA identified no index case (Sutherland et al, 1991). Another smaller study involving 55 patients in Cuba was also negative (Marrero-Gonzalez et al, 2003). However a study of 158 children with clinical presentation of LD from cerebral heteroplasia yielded a high incidence of 0.01% for BTD deficiency, which is at least 3 to 6 times higher than the general population (6.3 per 1000) (Zhang et al, 2007). The highest estimated incidence of BT deficiency in the European general population is 1:35000 (Möslinger et al, 2001). Even if the incidence of BTD is assumed to be ten times higher in the patients with LD /GDD, a minimum of 3500 patients would need to be screened to identify one index case.

The commonest symptoms of patients diagnosed with partial BTD were either neuro-developmental delay (87.5%) or neurological abnormalities (75%). Cutaneous manifestations such as dermatitis and hair loss were not represented in this cohort of patients. The commonest neuro-developmental and neurological symptoms reported in the two other cohorts of children from Iran and India were similar, consisting mainly of seizures (80-90%), sensorineural hearing loss, hypotonia and ataxia. They however reported more frequent presentation with cutaneous disorders (60 to 90%) including alopecia, non-specific rashes and seborrheic dermatitis (Karimzadeh et al 2013; Singh et al, 2015).

The most obvious limitation of our research is its retrospective design. A prospective study of patients randomised to either guideline implementation or clinical

opinion would be the most ideal method, given adequate resources such as a research grant.

A research grant for this type of study would be justified firstly, in view of the public health significance of childhood developmental disorders, affecting 1-3% of the population. Secondly, the real prevalence of BTD in children with LD/GDD is still unknown. Previous research on screening children with LD /GDD for BTD has been inconclusive and definite answers are still required for formulating evidence-based practice guidelines. Thirdly, it is unethical to miss any child with BTD, which is an easily treatable condition, with reversal of most symptoms if commenced early. Fourthly, though the literature suggest that the prevalence of BTD in children with GDD is higher than the general population, no definitive large population-based studies have been done to clarify the precise burden of this condition in this group of children (Ogundele, 2011). Hence larger, multicentre, multinational studies would be needed to clarify the true estimate of the incidence of BTD in pre-school children with LD /GDD.

Other limitations of this study need to be considered in interpreting the results. Firstly, this is a highly selective hospital-based population of referred patients with a high rate of neuro-developmental and neurological abnormalities. Secondly, this is a single centre study and may not be truly representative of the entire population in the country.

4. Conclusion

Following the introduction of an evidence-based protocol for investigation of children with global developmental delay, which recommended that biotinidase activities should be measured early in the investigation pathway for moderate or severe global developmental delay, the number of tests requested (monthly per 1000 live births) has progressively increased by more than 250% from 2008 to 2011. The finding of an annual incidence of partial BTD in this cohort of 138 patients (5.8%) which is several times higher than the estimated incidence of 0.008 (0.006 to 0.009) per 1000 live births in the developed countries, should be interpreted with caution due to inherent limitations of this study.

Moderate mental retardation is a recognised manifestation of cerebral dys-function in patients with profound BTD. We hypothesize that a relatively small number of children (actual number cannot be computed for lack of definitive research into the prevalence) would needlessly suffer a lifetime of chronic disabling neurological and or cutaneous disorders due to failure to screen them for BTD (Wolf, 2016). This is particularly of high relevance in the UK where a programme of newborn screening for BTD has not yet been implemented. These children would constitute a significant social burden and an unnecessary strain on the limited healthcare budget.

Until further multi-centre larger studies are available, it would appear justifiable that children with neurological and develop-mental disorders should be screened early for BTD to enable early commencement of treatment and reversal of most symptoms. Although the number of children to investigate for possible LD/GDD in order to diagnose one case of BTD may seem high, this investigation seems to be cost-effective, considering the life-time potentially very serious disabilities that may result if not identified (Vallejo-Torres et al, 2015).

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Table and Figures

Table 1. The annual rate of abnormal BT activity results and diagnosis of partial BTD [Ψ] deficiency

Year of study	No of Tests	Tests/mo/1000 live births**	No of Abnormal results*	Annual incidence of partial BTD [δ]
Jan-Dec 2008	21	0.31	2/21 (9.6%)	0.35
Jan-Dec 2009	29	0.43	3/29 (10.3%)	0.54
Jan-Dec 2010	38	0.57	1/38 (2.6%)	0.18
Jan-Oct 2011	62	1.11	4/62 (6.5%) ***	0.34
Total	**150**	**0.58**	**10/150 (6.7%)**	**0.357**

Key:

[Ψ] BTD=Biotinidase deficiency; BTA = Biotinidase Activity

* Reference levels of BT Activity: 2.1-8.2 or (3.1-8.1) nmol/ml/mn depending on age

** Based on the annual Live births rate (2008) of 5,595 and estimated mid-year population of 441.100

*** Two patients had normal results on repeat testing

[δ] Annual incidence per 1000 live births

Table 2. The Clinical presentation of patient with abnormal results

Categories of symptoms		No of Pts	% of Pts
Developmental /Neurobehavioral symptoms: (N = 7/8)	(Global) Developmental delay	5	62.5
	LD*	3	37.5
	ASD**	1	12.5
	Challenging behaviour	1	12.5
Neurological symptoms: (N =6/8)	Seizures/Epilepsy-	5	62.5
	Hearing loss	2	25
	Visual impairment	1	12.5
	Hypotonia	1	12.5
Other symptoms: (N = 2/8)	Cardiomyopathy, unexplained cardiac arrest, ICU [δ] admission	1	12.5
	Short stature	1	12.5
	Dysmorphism	1	12.5

Key:

Pts Patients

* Learning difficulties

** Autistic spectrum disorder

[δ] Intensive care unit

