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Biotinidase deficiency: What have we learned in forty years?

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ABSTRACT

Background: Biotinidase deficiency (BD) is an autosomal recessively inherited disorder that was first described in 1982. Forty years after its first description, we compiled available clinical data on BD with the aim of generating a more comprehensive picture of this condition.
Methods: A systematic search strategy was performed in relevant databases without limits for publication date or languages. We screened 3966 records and included 144 articles reporting individuals with BD and their clinical presentation as well as the outcomes, when available.
Results: This study included 1113 individuals with BD. More than half (51.5%) of these individuals were diagnosed by newborn screening, 43.3% in presence of clinical symptoms and 5.2% due to family screening. We grouped symptomatic individuals into four main clinical presentations: neonatal-onset (<1 month; 7.9%), early childhood-onset (<2 years; 59.2%), juvenile-onset (2–16 years; 25.1%) and adult-onset (>16 years; 7.7%). BD affected five main organ systems: nervous system (67.2%), skin (53.7%), eye (34.4%), auditory (26.9%) and respiratory system (17.8%). Involvement was mainly multisystemic (82.2%) of individuals, whereas isolated system presentation was seen in only 17.2% of individuals.
When reported, metabolic acidosis was present in 42.4% of symptomatic individuals and characteristic abnormal organic acid metabolites were found in 57.1%. Biotin treatment led to clinical stability or improvement in 89.2% of individuals. 1.6% of reported individuals with BD died due to non-availability of treatment or late diagnosis.
Conclusion: Newborn screening has had a major positive impact on the outcome of many individuals with BD. However, undiagnosed and non-treated BD remains a health concern. Given the risk of mortality or complications associated with late or missed diagnosis if newborn screening is not available, a trial of biotin should be considered in undiagnosed infants and adults exhibiting suspected clinical signs. Enzymatic activity and/or analysis of genetic variants can readily confirm the diagnosis of BD.

1. Introduction

Biotinidase deficiency (BD) is an autosomal recessively inherited metabolic disorder caused by pathogenic variants in the *BTD* gene resulting in reduced or absent biotinidase activity [1]. Biotinidase cleaves biotin from biocytin and biotinyl-peptides derived from protein-bound biotin, such as holocarboxylases, thereby recycling the vitamin [2]. Individuals with BD cannot recycle biotin, thereby resulting in secondary biotin deficiency [3]. In 1982, Wolf et al., showed that BD was the primary defect in most individuals with late-onset multiple carboxylase deficiency [2]. The initial clinical features of BD are variable, but most affected individuals develop neurological and cutaneous symptoms during childhood, including, but not limited to, seizures, hypotonia, ataxia, hearing loss, developmental delay, alopecia and skin rash [4]. Fortunately, daily administration of oral biotin can efficiently resolve many or most symptoms and prevent the development of symptoms in presymptomatic children, when initiated early [5].

Abbreviations: BD, Biotinidase deficiency; CT, Computerized tomography; EEG, Electroencephalogram; FLAIR, Fluid attenuated inversion recovery; MRI, Magnetic resonance imaging; NBS, Newborn screening; NMOSD, Neuromyelitis optica spectrum disorders; OA, Organic acids; PRISMA, Preferred reporting items for systematic Reviews and meta-analysis; WES, Whole exome sequencing; WHO, World health organization.

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A pilot program for newborn screening (NBS) of BD was initiated in Virginia in 1984 and screening was mandated in 1986 [6]. Over the years, all the other states in the United States and many countries have added BD to their NBS programs [7]. Because of this rapid implementation of NBS, the natural history of the disorder without treatment or with delayed treatment still is less well understood when compared to other metabolic diseases in which considerably more time has passed before they were incorporated into NBS programs. Forty years after BD was first discovered, we thought that it was important to review the existing published data about this disorder to better delineate its natural history, the impact of NBS and the long-term outcomes of biotin treatment in these enzyme-deficient individuals. We, therefore, conducted a comprehensive study and described the available reported clinical information related to BD over the past four decades with the aim of highlighting the relevant clinical aspects of one of the most readily treatable inherited genetic diseases.

2. Material and methods

A systematic search strategy was developed by a biomedical information specialist at Lausanne University Medical Library (JE), using a combination of controlled vocabulary terms and free text terms covering the two overarching concepts of the research: "biotinidase" and "deficiency". The search strategy was translated for the following databases: Medline Ovid ALL, Embase.com, PubMed, CINAHL with Full Text EBSCO, Central-Cochrane Library Wiley, Lilacs, and Web of Science Core collection. Supplementary searches were designed for Google Scholar, ProQuest Dissertations & Theses Global (PQDTGlobal), Dart Europe, and Base – Bielefeld University Library. The search strategies were peer reviewed by a second medical librarian before the searches were conducted on February 17, 2022. The searches were performed without limits for publication date or languages. The search equations for all the databases and search engines are provided as supplementary material. All references identified through the searches were downloaded and duplicates removed. The reviewers conducted citation searches on key studies.

Titles and abstracts followed by full-texts screening of all search results was performed by two independent reviewers for selection against the inclusion criteria using Rayyan [8]. Disagreements were resolved through discussion. Original human and clinical research articles on BD were eligible for inclusion without restriction of study design. Review articles and opinion papers, or abstracts were not considered in this study. We specifically included articles reporting individuals with BD and their clinical presentation as well as the outcomes, when available. We used a standardized data extraction sheet to extract relevant data from articles full-texts. Data regarding the age of diagnosis, diagnosis delay, BD type, zygosity, clinical status (symptomatic vs. asymptomatic), clinical presentation, management and outcomes were collected. Data on genotyping were not included in the scope of this study. Publications were classified according to their location using the world health organization (WHO) regional offices distribution and per decade. Ages of diagnosis were sorted into 12 different categories according to their clinical relevance. Partial BD was defined as having biotinidase enzyme activity between 10% and 30% of mean normal activity and profound BD as activity below 10% of mean normal activity [9]. The individuals' symptoms were divided into five main categories: neurological, dermatological, ophthalmological, audiological abnormalities and respiratory manifestations. We also reported biochemical features, imaging and electrophysiology. Characteristic organic acids were defined as the appearance of metabolites in urine suggestive of multiple carboxylase deficiency [10]. Missing data were designated as not reported in the study. We used descriptive statistics to summarize quantitative data while qualitatively describing the individuals' outcomes. The means and percentages were obtained using Microsoft Excel 2016. In addition, we provided a brief synthesis of the findings from specific subgroups, such as symptomatic adults with BD as well as those with partial BD that were symptomatic. Data were rounded to the nearest decimal. The protocol of this systematic study was pre-registered in the NIHR International Prospective Register of Systematic Reviews (link below).

https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020182059.

3. Results

3.1. Studies characteristics

This study includes 144 publications reporting 1113 individuals with BD. Fig. 1 shows the study's flowchart adapted from PRISMA 2020 flow diagram [11]. The number of publications about BD has continually increased since its first description forty years ago. Almost 40% of clinical publications have occurred during the last decade (Table 1). Eighty five percent of the publications have been case reports and case series with less than10 individuals. The majority of publications came from the European region (40.3%). Table 2 delineates the geographical distribution of publications included in this study.

3.2. Diagnosis context of individuals with BD

More than half (51.5%) of the individuals with BD included in this study were diagnosed by NBS, 5.2% of diagnosis was in the context of family screening after a positive diagnosis or a sibling and/or an offspring. The remaining 43.3% of individuals were symptomatic. Among diagnosed in presence of symptoms, 57.1% were diagnosed within their first year of life and 7.9% were detected before one month of age (Tables 3 & 4). 7.7% of these individuals were diagnosed during adulthood (>16 years). For clinical relevance, we grouped age of onset into four categories: neonatal-onset (<1 month): 7.9%, early childhood-onset (<2 years): 59.3%, juvenile-onset (2–16 years): 25.1%, adult-onset (>16 years): 7.7%.

We determined the geographical distribution of individuals with BD diagnosed by NBS and without NBS. As expected, regions that did not perform NBS (South-East Asian Region and Eastern Mediterranean Region) had the majority of their cases diagnosed by the presence of symptoms, as shown in Table 4.

Half of individuals with BD (50.7%) in this study did not have genetic analysis as shown in Table 5. This is probably because shortly after BD was discovered, genetic testing for variants was not available. Still today, the diagnosis is mainly confirmed by determining enzymatic activity.

Enzyme activity percentages were reported in 92% of the individuals with BD included in the review. A majority of the individuals had profound BD (57.8%). However, these data do not reflect the epidemiological distribution of the condition, but rather our study includes mostly case-reports. Therefore, there is a publication bias due to the publication of symptomatic cases with profound BD. Indeed, clinical cohort studies showed that partial BD is more frequent that profound BD [12–15].

3.3. Clinical presentation of individuals with BD

Symptoms were reported in 482 of 1113 individuals with BD (43.3%) and are summarized in Table 6. BD affected five main organs or systems: nervous system (67.2%), skin (53.7%), eye (34.4%), auditory (26.9%) and respiratory system (17.8%). 82.2% of individuals with BD had more than one system/organ affected at the time of diagnosis. The most common clinical presentation of BD was a combination of neurological and dermatological symptoms (48.1%). 9.3% of individuals with BD were reported with isolated ophthalmological findings.

When reported, metabolic acidosis was present in 42.4% of symptomatic individuals and characteristic abnormal organic acid metabolites were found in 57.1%. The characteristics metabolites were lactic acid, 3-methylcrotonic acid, 3-methylcrotonylglycine, 3-OH-propionic

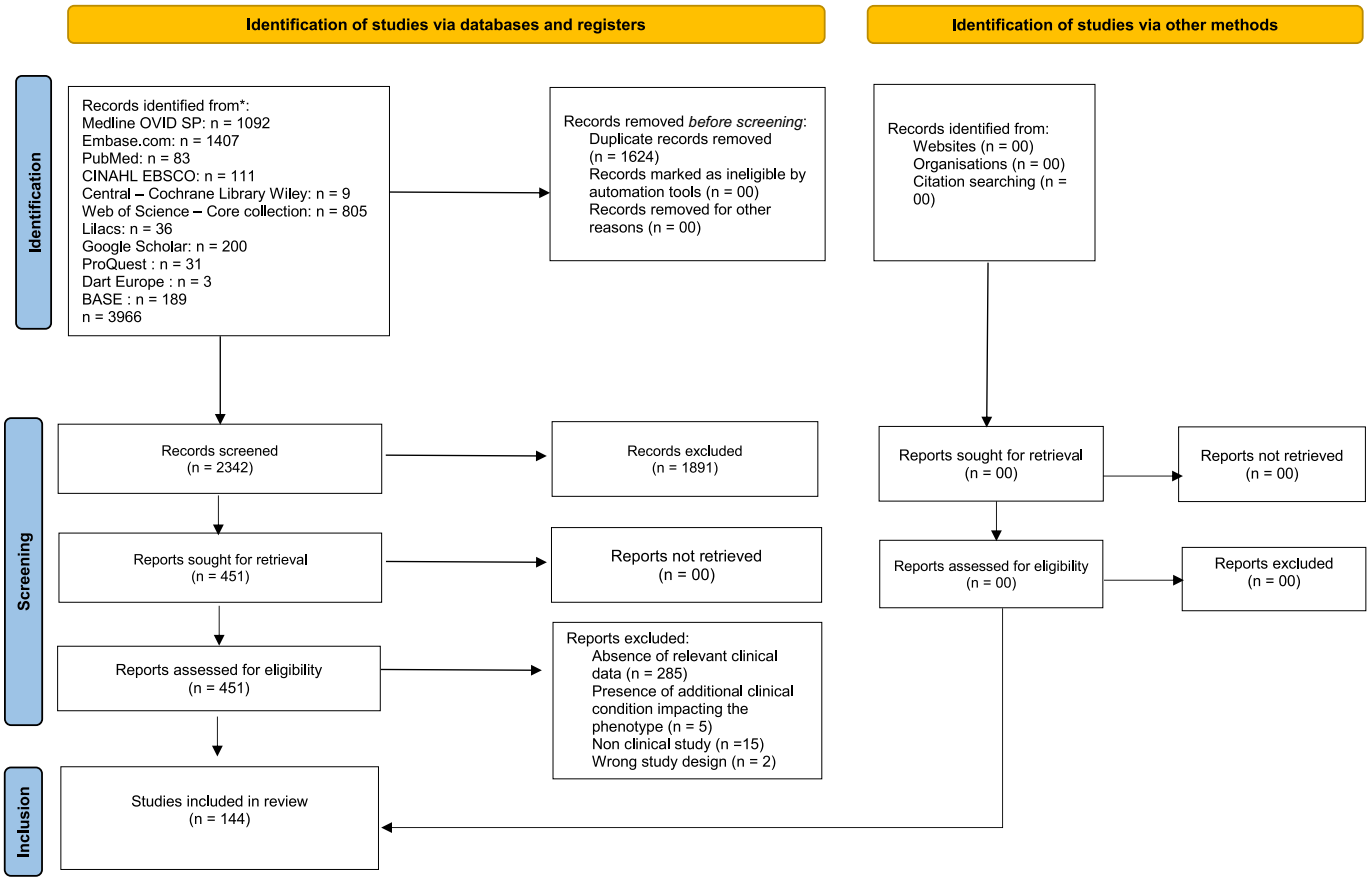

Fig. 1. : Flowchart of the review.

acid, methyl citric acid, and 3-hydroxyisovaleric acid, suggestive of multiple carboxylase deficiency.

The specific signs and symptoms exhibited at the time of diagnosis or during follow-up are shown in Table 7. Seizures, hypotonia and developmental delay were the most frequent neurological findings, whereas alopecia and rash were the more common dermatological findings. More than one third (34.4%) of the individuals presented with

Table 1
Publication decades of studies included ($n = 144$).

Decade of publication	n (%)
[1982–1992]	15 (10.4)
[1992–2002]	17 (11.8)
[2002−2012]	36 (25.0)
[2012−2022]	76 (52.8)
Total	144 (100.0)

Table 2
Geographical distribution of studies (n = 144).

WHO regions	N (%)
AFR	00 (0.0)
AMR	24 (16.6)
SEAR	24 (16.6)
EUR	63 (43.8)
EMR	23 (16.0)
WPR	10 (7.0)
Total	144 (100.0)

AFR: African region, AMR: Region of Americas; EMR: Eastern Mediterranean Region; EUR: European Region; SEAR: South-East Asian Region; WPR: Western Pacific Region.

Table 3
Age of diagnosis of individuals with BD diagnosed without NBS ($n = 540$).

Age of diagnosis	n (%)
1 week–1 mo	30 (5.6)
1 mo–3 mo	79 (14.6)
3 mo–6 mo	68 (12.6)
6 mo–1 yr	39 (7.2)
1–2 yr	38 (7.0)
2–10 yr	75 (13.9)
10–16 yr	20 (3.7)
16–18 yr	1 (0.2)
18–30 yr	18 (3.3)
30–45 yr	7 (1.3)
>45 yr	3 (0.6)
Not reported	162 (30.0)

Table 4
Geographical distribution of individuals with BD diagnosed with and without NBS.

WHO regions	Individuals with BD	NBS n (%)	Without NBS n (%)
AFR	00	0 (0.0)	0 (0.0)
AMR	433	264 (61.0)	169 (39.0)
SEAR	44	0 (0.0)	44 (100.0)
EUR	509	302 (59.3)	207 (40.7)
EMR	91	3 (3.3)	88 (96.7)
WPR	36	4 (11.1)	32 (89.9)
Total	1113	573 (51.5)	540 (48.5)

AFR: African region, AMR: Region of Americas; EMR: Eastern Mediterranean Region; EUR: European Region; SEAR: South-East Asian Region; WPR: Western Pacific Region.

Table 5
Genotype availability and zygosity.

Genotype	n (%)
Available	549 (49.3)
Not available	564 (50.7)
Total	1113 (100.0)
Available genotype	
Homozygotes	263 (47.9)
Compound heterozygotes	286 (52.1)
Total	549 (100.0)

Table 6
Signs and symptoms of individuals with BD ($n = 482$).

Systems or organs affected at the time of diagnosis	n (%)
Nervous system	324 (67.2)
Dermatological findings	259 (53.7)
Ophthalmological findings	166 (34.4)
Audiological abnormalities	130 (26.9)
Respiratory system findings	86 (17.8)
Multisystem clinical combinations at the time of diagnosis	**396 (82.2)**
Neuro-dermatological findings	222 (46.1)
Neuro-ophthalmological findings	7 (1.5)
Neuro-respiratory findings	8 (1.7)
Other combinations	159 (33.0)
Isolated clinical presentation	**83 (17.2)**
Only ophthalmological findings	45 (9.3)
Only neurological findings	19 (3.9)
Only audiological findings	14 (2.9)
Only respiratory findings	3 (0.6)
Only dermatological findings	2 (0.4)
Isolated biochemical abnormality	**3 (0.6)**

ophthalmological findings, mainly optic atrophy leading to visual loss in 17.0% of cases. Hearing loss was reported in 27.0% of the individuals. Breathing abnormalities, such as cough, dyspnea, or tachypnea occurred in 14.1% of cases.

Table 7
Signs and symptoms found at the time of diagnosis or during follow-up (n = 482).

Symptoms	n (%)
Neurological problems	**324 (67.2)**
Seizures	208 (43.2)
Hypotonia	154 (32.0)
Developmental delay	109 (22.6)
Ataxia	70 (14.5)
Lethargy	45 (9.3)
Muscle weakness	38 (7.9)
Gait abnormality	26 (5.4)
Encephalopathy	24 (5.0)
Developmental regression	19 (3.9)
Mental retardation	19 (3.9)
Dermatological findings	**259 (53.7)**
Rash	158 (32.8)
Alopecia	143 (29.7)
Seborrheic dermatitis	78 (16.2)
Hair loss/facial hair loss	48 (10.0)
Dry skin/desquamation	15 (3.1)
Eye involvement	**166 (34.4)**
Visual loss	82 (17.0)
Optic atrophy	82 (17.0)
Conjunctivitis	53 (11.0)
Scotoma	8 (1.7)
Hearing difficulties	**130 (27.0)**
Hearing loss	130 (27.0)
Respiratory problems	**86 (17.8)**
Breathing abnormalities	68 (14.1)
Infections	35 (7.2)

Table 8
Delay in diagnosis of symptomatic individuals with BD ($n = 135$).

Timeline of diagnosis	n (%)
Individuals with reported diagnosis delay (n = 482)	135 (28.0)
Delay (n = 135)	
<1 mo	42(31.1)
1–3 mo	42 (31.1)
3–6 mo	15 (11.1)
6–12 mo	7 (5.2)
>12 mo	29 (21.5)
Total	135 (100.0)

The duration between the appearance of the first symptoms and establishing the diagnosis was less than three months in about two-thirds of symptomatic individuals with BD (Table 8). Imaging of the brain and/or electrophysiological studies were reported in 32.8% of symptomatic individuals. 87.9% of these individuals had head magnetic resonance imaging (MRI) or computerized tomography (CT) scans and 46.5% had an electroencephalogram (EEG) because of seizures (Table 9). Despite the presence of neurological symptoms, 20.9% of brain imaging studies were normal. Similarly, almost one quarter of the EEGs (24.3 %) showed no abnormalities. Most common findings on brain MRI were symmetrical hyper-intensities on T2 weighted imaging affecting the white matter (leukoencephalopathy), enlarged ventricular spaces and brain atrophy. EEG abnormalities, in presence of seizures were highly nonspecific and variable; including excess slow wave activities, multifocal spike discharges and burst-suppression patterns. 1.4% of symptomatic individuals had normal urinary organic acids profile and no metabolic acidosis along with a normal MRI and EEG at the time of diagnosis.

3.4. Adult presentation of BD

We found 29 individuals diagnosed during adolescence or adulthood (>16 years old) with BD. These patients were aged between 19 and 63 years old at the time of diagnosis. Some exhibited no relevant medical history or symptoms until adulthood. Table 10 recapitulates the signs and symptoms of these adult individuals diagnosed with BD. Most frequent clinical findings in these patients were impaired consciousness, oppositional paratonia (resistance to passive movement), bilateral optic atrophy and sensorineural hearing loss, scaly and erythematous diffuse rashes, tetraparesis, spastic paraparesis, diplegia, bilateral horizontal nystagmus, ataxia and peripheral neuropathy.

These individuals often exhibited metabolic acidosis and/or characteristic organic acids, and when available, MRI of the brain showed diffuse hyper-intensive lesions (leukoencephalothy)on T2-weighted/ (FLAIR) images in the majority of them (6/11). Diagnosis was confirmed by enzyme activity and/or genetic analysis. Diagnosis of BD was initially missed in 5/29 of these adult individuals on clinical evaluation, but was later identified by whole exome sequencing (WES) analysis.

Table 9
Findings in symptomatic individuals with BD.

Brain imaging (Magnetic resonance imaging/ Computerized tomography)	($n = 139$)	n (%)
	Normal	29 (20.9)
	Abnormal	110 (80.1)
Electrophysiology (Electroencephalogram)	($n = 74$)	n (%)
	Normal	18 (24.3)
	Abnormal	56 (75.7)

Table 10
Signs and symptoms in individuals presenting with adult-onset BD ($n = 29$).

Signs/symptoms	n (%)
Neurological problems	**9 (31.0)**
Gait abnormality	7 (24.1)
Muscle weakness	4 (13.8)
Ataxia	3 (10.3)
Seizures	3 (10.3)
Developmental delay	2 (6.9)
Encephalopathy	2 (6.9)
Hypotonia	1 (3.4)
Eye involvement	**8 (27.6)**
Visual loss	7 (24.1)
Optic atrophy	7 (24.1)
Scotoma	3 (10.3)
Skin problems	**3 (10.3)**
Rash	2 (6.9)
Alopecia	1 (3.4)
Hearing difficulties	**2 (6.9)**
Hearing loss	2 (6.9)
Respiratory problems	**2 (6.9)**
Tachypnea	1 (3.4)
Infections	1 (3.4)

3.5. Clinical presentation of individuals with partial BD

This subgroup includes 384 individuals with partial BD of the 1113 regardless of the diagnosis context. We could not determine the exact proportion of patients with partial BD that present with symptoms due to inconsistency in many reports. However, we could summarize the frequency of each of the symptoms reported in this population. The most common symptoms were neurological (11.2%) and/or dermatological (9.6%) as shown in Table 11.

3.6. Management

3.6.1. How symptomatic individuals with BD were treated before diagnosis of BD

Various interventions were administered empirically in the presence of symptoms before the definitive diagnosis was made; this included antiepileptic drugs for seizures,corticosteroids for skin lesions, multi-vitamins and antibiotics (Table 12). Multivitamins were administered occasionally (3.9%), but the quantity of biotin contained in these preparations was not specified in the publications. However, most of the commercially available multivitamins contained biotin in the recommended dietary allowance dosages. Whether this small amount had an effect on the clinical phenotype was not clear.

Table 11
Signs and symptoms in individuals presenting with partial BD ($n = 384$).

Signs/symptoms	n (%)
Neurological problems	**43 (11.2)**
Seizures	20 (5.2)
Developmental delay	18 (4.7)
Hypotonia	6 (1.6)
Encephalopathy	5 (1.3)
Lethargy	4 (1.0)
Autism spectrum disorder	4 (1.0)
Ataxia	4 (1.0)
Muscle weakness	3 (0.8)
Mental retardation	2 (0.5)
Gait abnormality	1 (0.3)
Skin problems	**37 (9.6)**
Rash	16 (4.2)
Dry skin/desquamation	10 (2.6)
Seborrheic/diaper dermatitis	8 (2.1)
Hair loss/facial hair loss	8 (2.1)
Alopecia	7 (1.8)
Eye involvement	**6 (1.6)**
Optic atrophy	4 (1.0)
Visual loss	1 (1.0)
Conjunctivitis	1 (1.0)
Hearing difficulties	**14 (3.6)**
Hearing loss	14 (3.6)
Respiratory problems	**9 (2.3)**
Breathing signs	6 (1.6)
Infections	5 (1.3)

Table 12
Treatment(s) before the diagnosis of BD.

Management before diagnosis (n = 482)	n (%)
Any empirical treatment	**86 (17.8)**
Antiepileptic drugs	52 (10.8)
Immunoglobulins/corticoids	36 (7.5)
Multi-vitamins/zinc	19 (3.9)
Antibiotics	14 (2.9)

3.6.2. Management of symptomatic individuals following diagnosis of BD

Following the diagnosis of BD, most individuals were treated with biotin (5 mg, 10 mg or >10 mg per day). The most frequently administered dose was 10 mg/day as recommended for profound BD. In the five cases where an increased dose of biotin was reported, four had described an improvement during an intercurrent illness or acute presentation. However, these data are insufficient to support the existence of a dose-response effect in BD (Table 13).

3.7. Outcomes

In absence of a diagnosis of BD, 8.1% of individuals treated empirically improved, whereas the majority (57%) deteriorated as showed in Table 14. Improvement was reported in individuals exhibiting seizures who responded to antiepileptic drugs and in some cases to multivitamins given empirically.

Conversely, 89.2% of individuals treated with biotin showed clinical improvement or stability of their symptoms. When reported, 7 of 9 (77.8%) individuals demonstrated improvement on MRI after treatment with biotin. Most clinical symptoms, such as ataxia or muscle weakness, were reversible after treatment with biotin [16–19]. However, others, with hearing loss [20], optic atrophy [21–25] or mental retardation [26,27] did not improved after biotin treatment. Rare cases showed reversal of optic neuropathy [28,29].

Eighteen (18) deaths were reported among the 1089 individuals with reported outcomes in our study. The deaths were mostly due to a

Table 13
Biotin treatment of symptomatic individuals following diagnosis of BD.

Biotin treatment	n(%)
Individuals treated with biotin ($n = 1113$)	1060/1113 (95.2)
Individuals whose biotin dose has been reported ($n = 1060$)	459/1060 (43.3)
Different doses of biotin ($n = 459$)	
5 mg/d	95/459 (20.7)
10 mg/d	281/459 (61.2)
> 10 mg/d	83/459 (18.1)

Table 14
Clinical consequences of individuals with BD in the absence of diagnosis.

Evolution after first attitude w/o correct diagnosis ($n = 86$)	n (%)
Not reported	21 (24.4)
Improvement	7 (8.1)
Worsening/deterioration	49 (57.0)
Stabilization of symptoms	9 (10.5)
Total	86 (100.0)

Table 15
Survival and outcomes with biotin treatment.

Patient outcomes		n (%)
Individuals with outcomes reported		1089/1113 (97.8)
Clinical improvement/stability	Yes	971/1089 (89.2)
Death		18/1089 (1.6)
Improved MRI abnormalities	Yes	7/9 (77.8)
	No	2/9 (22.2)
Abnormalities on EEG	Yes	2/4 (50.0)
	No	2/4 (50.0)

delay in diagnosis or a lack of treatment during an acute presentation with severe complications, such as sepsis (3), respiratory distress (4) and multiple organ failure (2) (Table 15).

4. Discussion

BD is an emblematic example of an inborn error of metabolism that was rapidly integrated into many NBS programs worldwide after its identification because it readily met the basic criteria for inclusion in NBS [7]. Today, there is no doubt that the implementation of NBS has been a success and has influenced the successful outcomes of thousands of individuals with BD principally because the variability of presenting symptoms, failure to be added to the differential diagnosis and the effectiveness of a vitamin treatment. Despite this success, NBS is still not performed in many countries today and the diagnosis requires clinical awareness of the signs and symptoms of the disorder. By compiling and reviewing the clinical data from the 40-year literature on this disorder, we aimed to obtain a comprehensive demographic and clinical picture of the natural history of this disorder, including its initial manifestations, response to treatment and its outcomes with and without biotin treatment. We specifically did not intend to evaluate or discuss potential phenotype-genotype relationships in this study.

4.1. Onset and clinical presentation of BD

For clinical relevance, our data were grouped into four main clinical presentations. Besides the most frequent presentation during early childhood and adolescence [30], the first manifestations of BD may occur as early as during the neonatal period or as late as mid-adulthood. These neonatal- and adult-onset forms of BD together account for 15.6% of the reported symptomatic cases [22,23,29,31–34]. BD was diagnosed during the neonatal period (between one week and one month of age) following symptoms in 7.9% of individuals suggesting that some patients will likely develop clinical symptoms before the results of the NBS are available. Given that, severe and potentially life-threatening neurological manifestations may occur before the NBS results were available, BD should be considered in any newborn with unexplained neurological manifestations in areas where NBS is not performed. In areas with NBS, screening results should be available within 7–10 days of birth. Similarly, the disorder can be missed in adult individuals who present with characteristic manifestations of the disorder and were born before NBS was incorporated in the locations of their birth. Neurological and ophthalmological involvement including gait abnormalities, muscle weakness, ataxia, optic neuropathy and vision loss are the major findings in the adult-onset presentation [21,29,33–37]. This clinical picture in adult mimics *neuromyelitis optica spectrum disorders* (NMOSD) or multiple sclerosis. These similarities can unfortunately contribute to delay in the diagnosis of BD [28,37,38]. Some or all of these clinical features, including long-term manifestations, can be stabilized, improved or resolved with biotin treatment, highlighting the importance of rapid diagnosis [39–42].

4.2. Clinical suspicion and diagnosis of BD

We found that clinical symptoms of profound BD are non-specific and highly variable, but overall, the classical neuro-dermatological presentation remains the most frequent as described in the literature [7]. This study highlights the frequency of isolated ophthalmologic manifestations that affect almost 10% of individuals with BD. It also underscores specific presentations, such as neuro-respiratory issues in children and neuro-ophthalmological findings in adults that should prompt the testing for BD. It indicates that less common manifestations, such as recurrent infections, including conjunctivitis or pulmonary infections, can occur in some individuals [43,44]. In addition, most individuals with partial BD remain asymptomatic. However, when symptomatic, they likely exhibit typical neuro-dermatological findings or with atypical manifestations, such as autism spectrum behaviors [45–48].

Characteristics metabolites on organic acid analysis suggesting multiple carboxylases deficiency have historically been considered important biochemical features and clues to the diagnosis of BD and are used for the screening of suspected cases [1,30]. However, characteristic abnormal urinary organic acids, when reported, were found in only 57.1% of symptomatic individuals. This indicates that >40% of symptomatic individuals with BD would be missed if the diagnostic workup is based on detection of organic acids in urine only. In addition, in many instances, 3-hydroxyisovalerate was the only abnormal metabolite found on organic acid analysis [30]. Therefore, a normal organic acid profile does not exclude the diagnosis of BD.

Regarding imaging, bilateral and symmetrical leukoencephalopathy is the most frequent abnormality found on MRI, but brain imaging can be normal in up to 20% of cases even in presence of neurological manifestations [49]. Thus, BD should be considered in the differential diagnosis of unexplained leukoencephalopathy, especially in symptomatic adults [33].

Furthermore, a small number of individuals (1.5%) with BD had normal acid-base status, organic acid analysis, electrophysiology and brain imaging despite the presence of clinical symptoms. This emphasizes the need to perform enzymatic activity testing in clinically suspicious cases [18,47,50]. In the absence of NBS, diagnosis of BD was performed by enzymatic activity assay, more recently confirmed with genetic analyses. Although demonstration of genetic variants is useful, it is not mandatory to ascertain the diagnosis. The delay of diagnosis in symptomatic individuals with BD remains high with 21.5% diagnosed more than one year after the first clinical manifestations. This indicates that there still appears to be a considerable lag in time before many affected individuals are appropriately diagnosed and treated.

4.3. Management of individuals with BD

Among individuals with suspected BD, only 3.9% received empiric treatment with vitamins preparations or biotin before the diagnosis was confirmed [16,51–53]. Considering the importance of early treatment and the potential for irreversible complications of BD, this empirical treatment rate is low especially given that biotin supplementation is safe and does not affect the enzymatic assay used for diagnosis. Therefore, there is room for improvement in both clinical suspicion and initiation of treatment for BD especially in specific populations, such as neonates or adults presenting with unexplained neurological and/or ophthalmological findings. In areas were NBS is not performed, BD should be included in the differential diagnosis, especially in neonates or children presenting with neurological (i.e.refractory epilepsy) and/or unexplained skin manifestations that do not respond to conventional treatments (i.e., antiepileptic drug or corticoid treatment). We recommend starting biotin supplementation in these individuals immediately and monitor the response to this treatment. The treatment doses for symptomatic individuals varies between 5 and 20 mg/day, with 10 mg/day of biotin being the most often prescribed dose.

Wolf recently addressed many practical issues and questions regarding biotin therapy in children with BD that are valid for the adult populations as well [54]. Readers should refer to this article for specific information regarding biotin prescription, treatment and handling. Despite few reports of individuals taking higher doses of biotin at the time of diagnosis, we did not found sufficient evidence to support a clear dose-response effect of biotin in individuals with BD.

4.4. Outcomes

Most individuals with BD improved with biotin treatment and clinical manifestations was often reversible with early treatment. However, untreated BD can lead to irreversible complications, such as hearing loss [20], severe optic atrophy [21–25] or mental retardation [26,27]. These latter abnormalities appear to be stabilized after initiation of biotin treatment supporting the importance of treatment even in presence of already existing clinical complications. Interestingly, improvement in the leukoencephalopathy on MRI after treatment with biotin was observed in the majority of individuals [17,24,55–57]. Among reported individuals with BD, 1.6%died.These deaths were associated with late or delayed diagnosis or unavailability of biotin for treatment in some areas [21,31,33]. There were no deaths among individuals diagnosed by NBS and treated before clinical manifestations occurred. This observation further emphasizes the importance of NBS for the detection of individuals with BD before the onset of clinical symptoms, allowing early treatment, thereby avoiding potentially lethal or damaging complications. However, in absence of universal NBS, early clinical suspicion by clinicians remains the key that can help reduce the delay or failure to diagnosis this readily treatable condition.

4.5. Limitations

Despite the important information provided by this large dataset of BD cases, our review has some limitations that should be taken into consideration when interpreting these results. The first limitation is the fact that this study is descriptive, therefore, we cannot make reliable inference from the current data. This is mostly due to suboptimal data quality. Indeed, the data from this review were extracted from heterogeneous case reports and case series and do not constitute a suitable database for inferential or rigorous statistical analysis. This systematic review is dependent on available publications and, therefore, from quality and precision of information reported in those publications. For instance, some important information were not available in the majority of publications, especially quantitative data, such as absolute enzyme activity, accuracy of diagnosis delay, imaging studies and variant confirmation analysis. Lacking these data, greatly hampered our ability to perform statistical analyses. Similarly, given that we summarized published case reports and case series, there is an inherent selection bias towards individuals with serious and individuals with unusual clinical presentations, individuals who present at an older age and individuals with novel variants. This could explain the large number of non-classical presentations reported in this review, such as individuals with ophthalmological and respiratory involvement. Regional surveys and abnormally large populations in some countries with high rates of consanguinity also contribute to the ascertainment bias. Despite these limitations, this study has for the first time brought together all the available information on the biotinidase deficiency in the literature and extracted information that we believe are relevant not only for current clinical practice, but also for future studies.

4.6. Lessons learned and conclusion

Despite the above limitations, this extensive study of the literature on BD provided significant and relevant information for clinical practice. The highlights include the following:

1. NBS programs represent the most effective intervention for early diagnosis and treatment in order to avoid complications and avoidable mortality due to this disorder.
2. Given the risk of irreversible complications associated with late diagnosis and treatment, early empiric treatment with high doses (5-10 mg) of biotin in presence of clinical suspicion even before diagnostic confirmation is possible.
3. Our findings suggest that refractory epilepsy in neonates and NMOSD or multiple sclerosis in adults that do not respond to standard treatments should prompt the testing for BD.
4. Adult individuals born where NBS is not performed and presenting with unexplained neurological and/or ophthalmological manifestations (i.e., leukoencephalopathy, refractory epilepsy, gait abnormality and optic atrophy) should prompt the testing for BD.
5. Due to inconsistent or absent metabolic and imaging findings, BD can go undetected, therefore, enzymatic testing for biotinidase activity, possibly followed by genetic analysis should be performed in cases with a clinical suspicion for the disorder.
6. We suggest including BD gene in genetic panels for leukoencephalopathy and/or refractory epilepsy, because these findings may be the only manifestations of the disorder.

The growing awareness of this disorder and its systematic screening in many countries has had a major positive impact on the outcome of many individuals with BD. However, the mortality rate remains too high for a disorder that has been known for forty years and for which there is a simple, inexpensive and effective vitamin treatment. This supports the need to continue efforts to advocate NBS and the rapid initiation of biotin therapy.

Author's contributions

AT, GVW, and CT conceptualized the study, JE prepared and implemented the search strategy, AT, GVW and CT screened the records against inclusion criteria. AT, GVW and CT extracted and analyzed the data. AT, BW and CT drafted the manuscript/wrote the original draft. AT, ASF, BW and CT reviewed and edited the manuscript. All the authors read and approved the final version of this study.

Data availability

The dataset will be made available in a free access repository upon acceptation of the manuscript

Declaration of Competing Interest

The authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgme.2023.107560.

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