BMC Ophthalmology

Research article

The significance of opthalmologic evaluation in the early diagnosis of inborn errors of metabolism: the Cretan experience

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Published: 11 April 2002

BMC Ophthalmology 2002, **2**:2

Received: 2 October 2001
Accepted: 11 April 2002

This article is available from: http://www.biomedcentral.com/1471-2415/2/2

Abstract

Background: The Inborn Errors of Metabolism (IEM) are far from the rare systemic diseases that mainly affect the neural tissue. There are very few written reports on ocular findings in subjects with IEM, thus it was interesting to study the frequency of ocular findings in the studied population and explore their contribution to the early diagnosis of IEM.

Methods: Our study involved the evaluation of IEM suspected cases, which had been identified in a rural population in Crete, Greece. Over a period of 3 years, 125 patients, who fulfilled the inclusion criteria of this study, were examined. Analytical physical examination, detailed laboratory investigation as well as a thorough ocular examination were made.

Results: A diagnosis of IEM was established in 23 of the 125 patients (18.4%). Ten (43.5%) of the diagnosed IEM had ocular findings, while 8 of them (34.8%) had findings which were specific for the diagnosed diseases. One patient diagnosed with glycogenosis type 1b presented a rare finding. Of the 102 non-diagnosed patients, 53 (51.96 %) presented various ophthalmic findings, some of which could be related to a metabolic disease and therefore may be very helpful in the future.

Conclusions: The ocular investigation can be extremely useful for raising the suspicion and the establishment of an early diagnosis of IEM. It could also add new findings related to these diseases. The early management of the ocular symptoms can improve the quality of life to these patients.

Background

Until a few years ago, metabolic diseases, were thought to be controversial entities with exotic names, only a few people were involved in their research. The fact that the majority of these diseases were considered incurable reduced the interest of their investigation. However, recently the situation has changed dramatically and metabolic diseases have received serious attention and considerable

progress has been made in prevention and therapeutic management. It is now clear that metabolic diseases are far from rare. The incidence of metabolic diseases in North America and in Central and Northern Europe is 1:5000.

Metabolic diseases mainly affect the neural tissue, but may also affect others such as the heart, liver, kidneys, blood and eyes. The ocular symptoms and signs are found in a large number of these diseases [4]. They frequently represent an already allocated symptom of a systemic disorder. The ocular finding can rarely be so characteristic as to render itself the key to the diagnosis, as for example in Wilson's disease [5,6].

A pilot study has been implemented in rural Crete and its first results and experiences have been reported in a recent publication [7]. There are very few written reports on ocular findings in subjects with inborn errors of metabolism (IEM), thus it was interesting to study the frequency of ocular findings in the studied population and explore their contribution to the early diagnosis of IEM.

Methods

Our pilot study was carried out during the period from January of 1997 to January 2000. The predominant source of the study's data was derived from the eight Primary Health Care Centres in rural Crete, which accounts for 225,000 inhabitants, and are taking part in the activities of the Cretan Primary Healthcare Network [7]. An invitation was extended to all of the primary care physicians of these Health Centres, of which eight medical doctors participated in an intensive educational programme for IEM and their early diagnosis. A checklist with specific illness conditions, symptoms and clinical signs was drawn up (see additional file 1). Primary care physicians checked the presence of at least one condition, sign or symptom in all children or adults who visited the participating Health Centres and who had been symptomatic since childhood and were not related to other conditions. They referred all eligible subjects to the Department of Child Care at the University Hospital of Heraklion, Crete. Three of children who had examined at the Department of Ophthalmology at the University Hospital of Heraklion had fulfilled the inclusion criteria were added in our study sample. A full and analytical physical examination as well as a detailed laboratory investigation was made in this department. Patients with history of perinatal asphyxia, infection, injury or tumor of the central nervous system were excluded of the study. An ophthalmologic evaluation was part of this assessment. The ophthalmologic evaluation included the following:

(1) Case History (Personal and Family). (2) Visual acuity measurements for near and/or distant vision. In selecting the method of estimation of visual acuity we took into consideration factors such as age, existence of mental retardation, and collaboration of the patient. (3) Color Perception (using the Ishihara Isochromatic Cards). (4) Pupil reflexes (direct and indirect). (5) Near reflex. (6) Orthoptic evaluation including conjugate eye movements; cover-uncover test; cover-test and prism cover test where it was necessary. (7) Examination for presence of nystagmus. (8) Slit lamp examination of the anterior segment of the eye. (9) Retinoscopy. (10) Indirect ophthalmoscopy. (11) Photography when applicable.

The ocular investigation was performed every year on each patient included in the study.

Results

During the 3-year period the study involved the examination of 125 subjects which fulfilled the inclusion criteria of this study. There were 75 males (60%) and 50 females (40%). The ages were between 0 to 30 years. The mean age of the examined patients was 6.34 (S.D: ± 5.75) years. Of the 125 subjects examined, a diagnosis of IEM was established in 23 (18.4%). Subsequently 63 (50.4%) had ocular findings.

From the 23 diagnosed patients, 10 (43.5%) had ocular findings, and 8 of these (34.8%) had findings specific for the diagnosed diseases (see additional file 2). In one patient diagnosed with glycogenosis type 1b a rare finding of large preretinal spherical deposits near the ora serrata was documented. These deposits probably consisted of glycogen and/or triglycerides. To the best of our knowledge, this finding has not previously been reported in any publication.

Thirteen (56.5%) of the diagnosed patients had no ocular findings (5 patients with organic acidurias, 2 with glycogenosis type la, 2 b-oxidation defects, one with lysosomal disorder, one mitochondriopathy and two with aminoacid disorders).

From the 102 non-diagnosed patients 40 (39.21%) had no ocular findings and 9 (8.82%) had only a very low refractive error (-2.0D to + 2.0D). Fifty – three (51.96 %) undiagnosed patients presented various ophthalmic findings that are shown in (see additional file 3)

Discussion

This study attempted to show the significance of the ocular investigation in the early diagnosis and management of IEM. It is known that IEM affect vision because of the damage to the brain, visual pathways and other eye structures such as the lens, the cornea and the retina. The existence of the ocular finding was critical for the suspicion of the disease and the definitive diagnosis in several of the

diagnosed patients (18.4%). Of the 23 diagnosed patients, 10 (43, 47%) presented ocular symptoms (*Table 2*). In 4 patients (with Canavan's disease, metachromatic leucodysrtophy and adrenoleucodystrophy) the suspicion of the disease was set because of the other clinical symptoms in spite of the fact that atrophy of the optic nerve was a specific finding [8]. In 8 (34,78%) of the 10 diagnosed patients the ocular symptoms were specific for the underlying disease. This means that 80% (8/10) of the patients diagnosed with ocular symptoms had specific ocular findings for the diagnosed disease.

The diagnosis of IEM represents one of the most difficult aspects of medicine and their differential diagnosis from perinatal lesions is not always easy. In this case, the ocular findings can be of great value in directing the diagnosis to a specific disease. This was the case with one of our patients with Niemman-Pick type C who had a very slow progression. It was the ocular findings (vertical gaze paresis, doll's eye movements and retinitis pigmentosa) which led to the suspicion of the diagnosis [9,11].

In the cases of the patients with Kearns-Sayre syndrome, mannosidosis and Lowe's syndrome the ocular findings were characteristic for the disease and contributed to the fast diagnosis of the underlying disease. The patient with the Kearns-Sayre syndrome exhibited the typical triad of progressive external ophthalmoplegia, retinal pigmentary degeneration, and heart block [12,14]. The patient with Mannosidosis presented a progressively developing wheel-like cataract and optic disk pallor [15,16] which was probably related to demyelination and associated gliosis involving the parieto-occipital white matter [17]. The patients mother was at the first trimester of her 2nd pregnancy. Prenatal screening was ordered which revealed the some diagnosis in the fetus [18]. The patient in Lowe's syndrome (oculocerebrorenal syndrome) presented congenital discoid cataracts [19,20], miosis, congenital glaucoma [21]. The mother had flake like opacities of the lenses, a typical finding in a female carrier [22]. The child was treated for cataracts, and glaucoma. Currently, he is under topical therapy with a b-blocker.

In biotinidase deficiency, strabismus is a non-specific ocular finding. However, it is described in 30% of the patients in various research studies [23,24].

The case of a patient with glycogenosis type 1b is of interest. This patient presented large preretinal spherical deposits near the ora serrata, probably consisting of glycogen and/or triglycerides. This patient was under no therapeutic scheme until the age of 25. Three years later in a new fundus examination the large preretinal deposits were absorbed and replaced with small drussen-like preretinal deposits. These new deposits were mainly concentrated in the peripheral retina of the inferior nasal quadrant of each eye. Our ocular finding in glycogenosis type 1b may be correlated with ocular findings reported by other authors for this disease. [25].

It is an interesting fact that although 18.4% were finally diagnosed, but ocular findings existed in 50.4% of them.

The findings in undiagnosed patients were notable. A high percentage of ocular findings were documented for these patients (51.96%) A tight surveillance of the undiagnosed patients is important as some of these findings may be related to a metabolic disease, the existence of which can not be established at the present time although it is certain that some of these findings should be very helpful in the future.

The high percentage of ocular findings (43.47% in the diagnosed and 51.96% in the undiagnosed patients) in both diagnosed and undiagnosed patients is indicative of the significant involvement of the eye in problems raising a suspicion of an IEM disease. The ocular evaluation of these patients seems to be obligatory.

Conclusions

The results of this study demonstrate that a thorough ophthalmologic examination can be extremely useful for the pediatricians and the neurologist concerning the diagnosis of metabolic neurogenetic diseases. For the establishment of the diagnosis, the collaboration of various institutes is usually necessary in some cases the diagnosis can be facilitated by the ophthalmologic findings. Moreover, there are cases where an ophthalmologic examination is the main examination that leads to the early recognition of these diseases. Finally, the amelioration of the ocular symptoms can offer a better quality of life to those patients.

Competing Interests

None declared.

Author controibutions

Dr Tsagaraki Daria and Dr Evangeliou Athanasios had primary responsibility for protocol development, patient screening, enrolment, outcome assessment, preliminary data analysis and writing of the manuscript. **Dr Tsilibaris Miltiadis, Dr Spilioti Martha and Dr Lionis Christos** participated in the development of protocol and analytic framework of the study and contributed to the writing of the manuscript. **Dr Michailidou Eleni** was responsible for patient screening and **Dr Pallicaris Ioannis** supervised the design and execution of the study and contributed to the writing of the manuscript.

Additional material

Additional file 1

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Additional file 2

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Additional file 3

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Pre-publication history

The pre-publication history for this paper can be accessed here:

http://www.biomedcentral.com/1471-2415/2/2/prepub