Chapter 9

Pseudo Toxoplasmosis

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Additional information is available at the end of the chapter

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1. Introduction

Signs that may be included in the clinical presentation of congenital toxoplasmosis may be observed in infants without identification of *Toxoplasma gondii* or other intrauterine infection. When congenital toxoplasmosis is excluded, these case are diagnosed as having pseudo toxoplasmosis (Hervouet, 1961), pseudo-TORCH (*toxoplasma*, rubella, cytomegalovirus, and herpes simplex) syndrome (Baraitser et al., 1983; Burn et al., 1986; Cohen et al., 2012; Ishitsu et al., 1985; Knoblauch et al., 2003; Kulkarni et al., 2010; Nakamura et al., 2011; Reardon et al., 1994; Vivarelli et al., 2001; Watts et al., 2008; Wieczorek et al., 1995) or congenital infection-like syndrome (Abdel-Salam & Zaki, 2009; al-Dabbous et al., 1998; al-Gazali et al., 1999; Dale et al., 2000; Knoblauch et al., 2003; Kulkarni et al., 2010; Mishra et al., 2002; Mizuno et al., 2011; Slee et al.,1999).

These signs include microcephaly (Aalfs et al., 1995; Abdel-Salam & Zaki, 2009; Abdel-Salam et al., 1999; Abdel-Salam et al., 2000; Ahmadi & Bradfield, 2007; Aicardi & Goutières, 1984; al-Dabbous et al., 1998; al-Gazali et al., 1999; Alzial et al., 1980; Angle et al., 1994; Atchaneeyasakul et al., 1998; Baraitser et al., 1983; Bogdan, 1951; Book et al., 1953; Briggs et al., 2008; Burn et al., 1986; Cantú et al., 1977; Casteels et al., 2001; Dale et al., 2000; Eventov-Friedman et al., 2009; Feingold & Bartoshesky 1992; Fisch et al., 1973; Fryns et al., 1995; Hoyeraal et al., 1970; Hordijk et al., 1996; Hreidarsson et al., 1988; Ishitsu et al., 1985; Jarmas et al., 1981; Kloepfer et al., 1964; Knoblauch et al., 2003; Komai et al., 1955; Kozma et al., 1996; Kulkarni et al., 2010; Leung, 1985; Limwongse et al., 1999; McKusick et al., 1966; Mishra et al., 2002; Nakamura et al., 2011; Nemos et al., 2009; Ostergaard et al., 2012; Pearson et al., 2008; Reardon et al., 1994; Sadler & Robinson, 1993; Simonell et al., 2002; Slee et al., 1999; Strauss et al., 2005; Tenconi et al., 1981; Trzupek et al., 2007; van den Bosch, 1959; van Genderen et al., 1997; Vasudevan et al., 2005; Vivarelli et al., 2001; Warburg & Heuer, 1994; Wieczorek et al., 1995), intracranial calcifications (Abdel-Salam & Zaki, 2009; Aicardi & Goutières, 1984; al-Dabbous et al., 1998; al-Gazali et al., 1999; Asai et al., 2012; Baraitser et al., 1983; Bogdan, 1951; Briggs et al., 2008; Burn et al., 1986; Cohen et al., 2012; Dale et al., 2000;

Hervouet, 1961; Ishitsu et al., 1985; Knoblauch et al., 2003; Kulkarni et al., 2010; Mishra et al., 2002; Mizuno et al., 2011; Nakamura et al., 2011; Reardon et al., 1994; Revesz et al., 1992; Slee et al., 1999; Vivarelli et al., 2001; Watts et al., 2008; Wieczorek et al., 1995) and retinal changes (Abdel-Salam et al., 1999; Abdel-Salam et al., 2000; Ahmadi & Bradfield, 2007; Alzial et al., 1980; Angle et al., 1994; Asai et al., 2012; Atchaneeyasakul et al., 1998; Bogdan, 1951; Burn et al., 1986; Cantú et al., 1977; Casteels et al., 2001; Eventov-Friedman et al., 2009; Feingold & Bartoshesky 1992; Fryns et al., 1995; Hervouet, 1961; Hordijk et al., 1996; King et al., 1998; Limwongse et al., 1999; McKusick et al., 1966; Revesz et al., 1992; Sadler & Robinson, 1993; Simonell et al., 2002; Strauss et al., 2005; Tenconi et al., 1981; Trzupek et al., 2007; van Genderen et al., 1997; Vasudevan et al., 2005; Warburg & Heuer, 1994; Watts et al., 2008).

The majority of the cases have a family history (Abdel-Salam & Zaki, 2009; Aicardi & Goutières, 1984; al-Dabbous et al., 1998; al-Gazali et al., 1999; Alzial et al., 1980; Atchaneeyasakul et al., 1998; Baraitser et al., 1983; Bogdan, 1951; Book et al., 1953; Briggs et al., 2008; Burn et al., 1986; Cantú et al., 1977; Cohen et al., 2012; Dale et al., 2000; Fisch et al., 1973; Hordijk et al., 1996; Ishitsu et al., 1985; Jarmas et al., 1981; Knoblauch et al., 2003; Kozma et al., 1996; Leung, 1985; Limwongse et al., 1999; McKusick et al., 1966; Reardon et al., 1994; Sadler & Robinson, 1993; Simonell et al., 2002; Slee et al., 1999; Trzupek et al., 2007; van Genderen et al., 1997; Vivarelli et al., 2001; Warburg & Heuer, 1994), and thus a genetic basis has been proposed.

To diagnose the clinical entities described below, evidence of congenital infection including toxoplasmosis is the most important exclusion criterion. Misdiagnosis would result in erroneous counseling as to risk of recurrence (Aicardi et al., 2012).

2. Clinical entities

2.1. Aicardi syndrome

2.1.1. Overview

Aicardi syndrome (MIM: 304050) is a congenital disorder characterized by a triad of signs, including corpus callosum agenesis, severe epilepsy, and chorioretinal lacunae (Aicardi et al., 1965; Dennis & Bower, 1972).

2.1.2. History

In 1965, Aicardi et al. reported eight female infants with spasms in flexion, callosal agenesis and various ocular abnormalities. In 1972, Dennis & Bower also reported a female patient and established the Aicardi Syndrome.

2.1.3. Genetics

The Aicardi syndrome is believed to an X-linked dominant disorder lethal to males and the cases of Aicardi syndrome are female infants, and males with the XXY genotype (Hopkins et

al., 1979). Mutations in the CDKL5 gene on chromosome Xp22 have been found in these patients (Nemos et al., 2009).

2.1.4. Differential diagnosis

Although the Aicardi syndrome normally has a poor prognosis, there is a heterogeneity of clinical severity. A mild case of a chorioretinal defect and a hypoplastic disc has been reported (King et al., 1998). The case was misdiagnosed as having cerebral and retinal toxoplasmosis.

The presence of corpus dysgenesis supports the diagnosis of Aicardi syndrome. In addition, the Aicardi syndrome does not cause intracranial calcifications which are likely to be present in cases of congenital toxoplasmosis (Table 1). Ocular abnormality is various, however, chorioretinal lacunae are thought to be pathognomonic.

		inheritance	microcephaly	intracranial calcification	retinal changes	
2.1	Aicardi Syndrome MIM: 304050	X-linked dominant	+	-	+ (chorioretinal lacuna)	corpus agenesis
2.2	Aicardi-Goutières Syndrome (AGS) MIM: 225750, 610181, 610329, 610333, 612952	autosomal recessive	+ (post-natal)	+ (basal ganglia)	-	CSF lymphocytosis
2.3	Hoyeraal-Hreidarsson syndrome (HHS) MIM: 300240	X-linked recessive	+	-	-	severe aplastic anemia
2.4	Microcephaly, lymphedema, chorioretinal dysplasia syndrome (MLCRD) MIM: 152950	autosomal dominant	+	-	+ (chorioretinal dysplasia)	pedal lymphedema
2.5	Microcephaly and chorioretinopathy with or without mental retardation, autosomal recessive MIM: 251270	autosomal recessive	+	-	+ (chorioretinal dysplasia)	
2.6	Pseudo-TORCH syndrome (narrowly-defined) MIM: 251290	autosomal recessive	+	+	-	overlapping with AGS (2.2)
2.7	Revesz syndrome MIM: 268130	autosomal dominant	not apparent	+	+ (exudative retinopathy)	severe aplastic anemia
	congenital toxoplasmosis	-	+	+	+	

Table 1. Clinical findings of the patients affected by congnetial toxoplasmosis and the pseudo toxoplasmosis

2.2. Aicardi-Goutières Syndrome (AGS)

2.2.1. Overview

The AGS is a rare neurodevelopmental genetic disorder associated with intracranial calcification, leukocytosis in the cerebrospinal fluid (CSF), and microcephaly. (Aicardi & Goutières, 1984; Aicardi et al., 2012)

2.2.2. History

In 1984, Aicardi & Goutières reported eight infants with spasticity, acquired microcephaly, bilateral symmetrical calcifications in the basal ganglia and chronic CSF lymphocytosis in five consanguineous families.

2.2.3. Genetics

Approximately 90% of individuals with characteristic findings of AGS have been found to have mutations in the TREX1 gene on chromosome 3p21.31 (AGS1, MIM: 225750), RNASEH2A gene on chromosome 19p13.2 (AGS4, MIM: 610333), RNASEH2B gene on chromosome 13q14.3 (AGS2, MIM: 610181), RNASEH2C gene on chromosome 11q13.1 (AGS3, MIM: 610329), and SAMHD1 gene on chromosome 20q11.23 (AGS5, MIM: 612952). (Aicardi et al., 2012)

Mutations in TREX1 have also been found in some patients with systemic lupus erythematodes (SLE). Siblings with SLE who present with congenital infection-like intracranial calcification (Dale et al., 2000), may be associated with AGS. (Aicardi et al., 2012) It has also been suggested that the narrowly-defined pseudo-TORCH syndrome (2.6) shows a phenotypic overlap and that most cases of pseudo-TORCH syndrome are in fact AGS. (Aicardi et al., 2012)

2.2.4. Differential diagnosis

In case of AGS, leukocytosis in the CSF and increased concentrations of interferon-alfa (IFN-α) in the CSF are found (Aicardi et al., 2012) and microcephaly is absent at birth (Aicardi & Goutières, 1984). The onset occurs at 3-6 months of age in many patients.

Ocular structures are almost invariably normal on examination. (Aicardi et al., 2012) (Table 1)

2.3. Hoyeraal-Hreidarsson syndrome (HHS)

2.3.1. Overview

The HHS (MIM: 300240) is a severe multisystemic disorder with pre- and postnatal growth retardation, progressive pancytopenia, microcephaly, and cerebellar hypoplasia. (Aalfs et al., 1995; Knight et al., 1999; Pearson et al., 2008)

2.3.2. History

In 1970, Hoyeraal et al. reported two brothers with hypoplastic thrombocytopenia, microcephaly and cerebral malformations. In 1988, Hreidarsson et al. also reported an affected boy. In 1995, Aalfs et al. reported another male patient and proposed to use the eponym HHS. The first symptoms of pancytopenia did not occur before the age of five months and continued to deteriorate for years, despite extensive therapeutic measures.

2.3.3. Genetics

Mutations in the DKC1 gene on chromosome Xq28 have been found in the patients including the family reported by Aalfs et al. in 1995. (Knight et al., 1999) The gene is also responsible for X-linked dyskeratosis congenita (DKC, MIM: 305000), an inherited bone-marrow-failure syndrome characterized by skin pigmentation, nail dystrophy and leucoplakia which usually develop towards the end of the first decade of life. The HHS is revealed to be a severe variant of DKC. (Knight et al., 1999; Pearson et al., 2008)

2.3.4. Differential diagnosis

The HHS is marked by severe aplastic anemia. While retinopathy can be induced by anemia, ocular abnormality or intracranial calcification is not usually observed in cases of HSS. (Table 1)

2.4. Microcephaly, lymphedema, chorioretinal dysplasia syndrome (MLCRD)

2.4.1. Overview

As its name implies, the MLCRD (MIM: 152950) is characterized by a triad of signs including microcephaly, lymphedema, and chorioretinal dysplasia. (Angle et al., 1994; Casteels et al., 2001; Eventov-Friedman et al., 2009; Feingold & Bartoshesky 1992; Fryns et al., 1995; Limwongse et al., 1999; Ostergaard et al., 2012; Strauss et al., 2005; Vasudevan et al., 2005). Mental retardation is also usually present. Different combinations of these signs inherited in an autosomal dominant pattern have been reported (Leung, 1985; Hordijk et al., 1996; Simonell et al., 2002). Cases with these signs have been assumed to belong to the same spectrum of genetic disorders.

An autosomal recessive form of microcephaly with chorioretinopathy (McKusick et al., 1966) has been reported and categorized as microcephaly and chorioretinopathy with or without mental retardation, autosomal recessive (MIM: 251270) (2.5).

2.4.2. History

In 1981, Tenconi et al. reported patients with microcephaly and chorioretinopathy in an autosomal dominant pattern, and Jarmas et al. reported two brothers with microcephaly and retinal folds. In 1985, Leung investigated the combination of microcephaly and lymphedema

in at least 4 generations of a Chinese family. In 1992, Feingold & Bartoshesky described two unrelated boys with microcephaly, lymphedema and chorioretinal dysplasia and proposed that the combination represents a single syndrome.

2.4.3. Genetics

Mutations in the KIF11 gene on chromosome 10q23 have been identified in some patients with the MLCRD. (Ostergaard et al., 2012)

2.4.4. Differential diagnosis

Congenital lymphedema is confined to the dorsa of the feet (Angle et al., 1994; Casteels et al., 2001; Eventov-Friedman et al., 2009; Feingold & Bartoshesky 1992; Fryns et al., 1995; Leung, 1985; Limwongse et al., 1999; Strauss et al., 2005; Vasudevan et al., 2005) and this is hardly observed in cases of congenital toxoplasmosis. (Table 1)

Intracranial calcifications, which are likely to be present in cases of congenital toxoplasmosis are not observed in cases of MLCRD. (Table 1)

2.5. Microcephaly and chorioretinopathy with or without mental retardation, autosomal recessive

2.5.1. Overview

While the combination of microcephaly and chorioretinopathy with or without mental retardation can be caused by heterozygous mutation in the KIF11 gene known as MLCRD (MIM: 152950) (2.4), autosomal recessive inheritance has also been suggested in familial cases (McKusick et al., 1966). A discovery of causative homozygous mutation (Puffenberger et al., 2012) has proved the independent entity, microcephaly and chorioretinopathy with or without mental retardation, autosomal recessive (MIM: 251270).

2.5.2. History

The role of consanguinity in congenital microcephaly was repeatedly reported (Kloepfer et al., 1964; Komai et al., 1955; van den Bosch, 1959). In 1966, McKusick et al. described eight individuals of microcephaly in two sibships of an imbred group. All of them had pigmentary abnormality of the fundus with mental retardation.

2.5.3. Genetics

A homozygous mutation in the TUBGCP6 gene on chromosome 22q13.33 was found in four cases reported by McKusick et al. in 1966. (Puffenberger et al., 2012)

2.5.4. Differential diagnosis

Microcephaly and chorioretinopathy with or without mental retardation, autosomal recessive produces the symptoms similar to those of the MLCRD (MIM: 152950) spectrum

(2.4). Intracranial calcifications are not observed as in MLCRD. (Table 1) Lymphedema is considered to be pathognomonic for the MLCRD, has not been reported in cases of Microcephaly and chorioretinopathy with or without mental retardation, autosomal recessive. (Table 1)

2.6 Pseudo-TORCH syndrome (narrowly-defined)

2.6.1. Overview

Narrowly-defined pseudo-TORCH syndrome (al-Dabbous et al., 1998; Baraitser et al., 1983; Briggs et al., 2008; Burn et al., 1986; Cohen et al., 2012; Ishitsu et al., 1985; Knoblauch et al., 2003; Kulkarni et al., 2010; Nakamura et al., 2011; Reardon et al., 1994; Vivarelli et al., 2001; Watts et al., 2008; Wieczorek et al. 1995), also called Baraitser-Reardon syndrome (Vivarelli et al., 2001), or band-like calcification with simplified gyration and polymicrogyria (BLCPMG; MIM: 251290) (Abdel-Salam & Zaki, 2009; Briggs et al., 2008; O'Driscoll et al., 2010), is associated with microcephaly and intracranial calcifications mimicking congenital toxoplasmosis in the absence of infection.

2.6.2. History

In 1983, Baraitser et al. reported two brothers with microcephaly and intracranial calcifications. The bilateral symmetrical calcification was in white matter and thalamus. In 1994, Reardon et al. reported nine patients from four families with microcephaly, intracranial calcifications and CNS disease and described them as "congenital intrauterine infection-like syndrome".

In 2001, Vivarelli et al. reported five patients in three families and proposed to use the eponym, Baraitser-Reardon syndrome. In 2008, Briggs et al. also reported five patients in three families with a pattern of BLCPMG as a distinct "pseudo-TORCH" phenotype.

2.6.3. Genetics

Mutations in the OCLN gene on chromosome 5q13.2 have been found in a part of affected individuals, categorized as BLCPMG. (O'Driscoll et al., 2010) A part of the cases of the pseudo-TORCH syndrome without the OCLN mutation may in fact be cases of Aicardi-Goutières Syndrome (2.2). (Aicardi et al., 2012)

2.6.4. Differential diagnosis

As some cases of pseudo-TORCH syndrome are thought to be in fact AGS (Aicardi et al., 2012), there is a phenotype overlap between pseudo-TORCH syndrome and AGS (2.2).

Ocular changes are not reported with pseudo-TORCH syndrome / AGS. (Table 1)

2.7. Revesz syndrome

2.7.1. Overview

Revesz syndrome (MIM: 268130), also known as cerebroretinal microangiopathy with calcifications and cysts (CRMCC) is a rare and fatal disorder, characterized by intrauterine growth retardation, bilateral exudative retinopathy, intracranial calcification and cysts. (Asai et al., 2012; Revesz et al. 1992; Savage et al., 2008)

2.7.2. History

In 1992, Revesz et al. reported a 6-month old boy presenting with bilateral leucocoria. The retinal appearance resembled Coat's disease. Widespread grey and white matter calcification in the brain and severe aplastic anemia were also noted. His platelet count eventually became impossible to control and the patient died at 19 months of age. In 1994, Kajtár & Méhes reported the second case, a 2-year old girl with thrombocytopenic purpura and bilateral progressive Coats'-like retinopathy.

2.7.3. Genetics

A heterozygous mutation in the gene encoding TRF1-interacting nuclear factor-2 (TINF2) on chromosome 14q12 has been found in a case of Revesz syndrome. (Savage et al., 2008) Another heterozygous truncating mutation in the TINF2 gene has been identified in a case. (Sasa et al., 2012) TINF2 is a component of the shelterin telomere protection complex, TINF2 mutations result in very short telomeres.

An inherited bone marrow failure syndrome, dyskeratosis congenital-3 (MIM: 613990) is also caused by the mutations in the TINF2 mutations.

2.7.4. Differential diagnosis

While Revesz syndrome marked by the severe aplastic anemia is related to HHS (2.3), Revesz syndrome causes Coats'-like retinopathy and intracranial calcification. A case reported as "congenital infection-like syndrome with intracranial calcification" (Mizuno et al., 2011) may be a case of Revesz syndrome. (Asai et al., 2012)

Coats'-like retinopathy is exudative, easily distinguishable from chorioretinal lacunae or dysplasia on ophthalmoscopy. (Table 1)

3. Pseudo-pseudo toxoplasmosis

3.1. Background

Even though clinical differential diagnosis summarized in Table 1 can be helpful, there are exceptions. A case of congenital toxoplasmosis can have the look of one of pseudo toxoplasmosis entities. A serological investigation for toxoplasmosis also has its indications and limitations. (Johnson et al., 1993).

3.2. Case report

A male infant was delivered by Cesarean section at 37 weeks of gestation. (Ozeki et al., 2010) There was no family history for microcephaly, retinitis pigmentosa or consanguinity. The mother was type 1 diabetic and had once experienced an intrauterine fetal death. At 20 weeks pregnant, microcephaly had been detected by ultrasonography. Toxoplasmosis had been suspected, but the treatment was withheld because of only a slightly elevated maternal *Toxoplasma* specific immunoglobulin M (IgM) antibody, 1.4 index by enzyme linked immnosorbent assay (ELISA) and a borderline IgG avidity index, 50% at 28 weeks pregnant.

The infant weighing 2,858 g with Apgar score 9/10, respectively, had microcephaly, marked lymphoedema of dorsum of both feet and chorioretinal dysplasia in the both eyes (Figure 1). The electroretinogram was nearly nonrecordable. A computed tomography (CT) scan was negative for brain calcifications or hydrocephalus. Hepatic calcifications, splenomegaly, and ascites were not noted. *Toxoplasma* IgM (ELISA) was negative (0.1 index) while IgG was positive (70 index).

Toxoplasma gondii DNA was detected in the serum by polymerase chain reaction (PCR) (Figure 1(d)) to confirm the diagnosis of congenital toxoplasmosis.

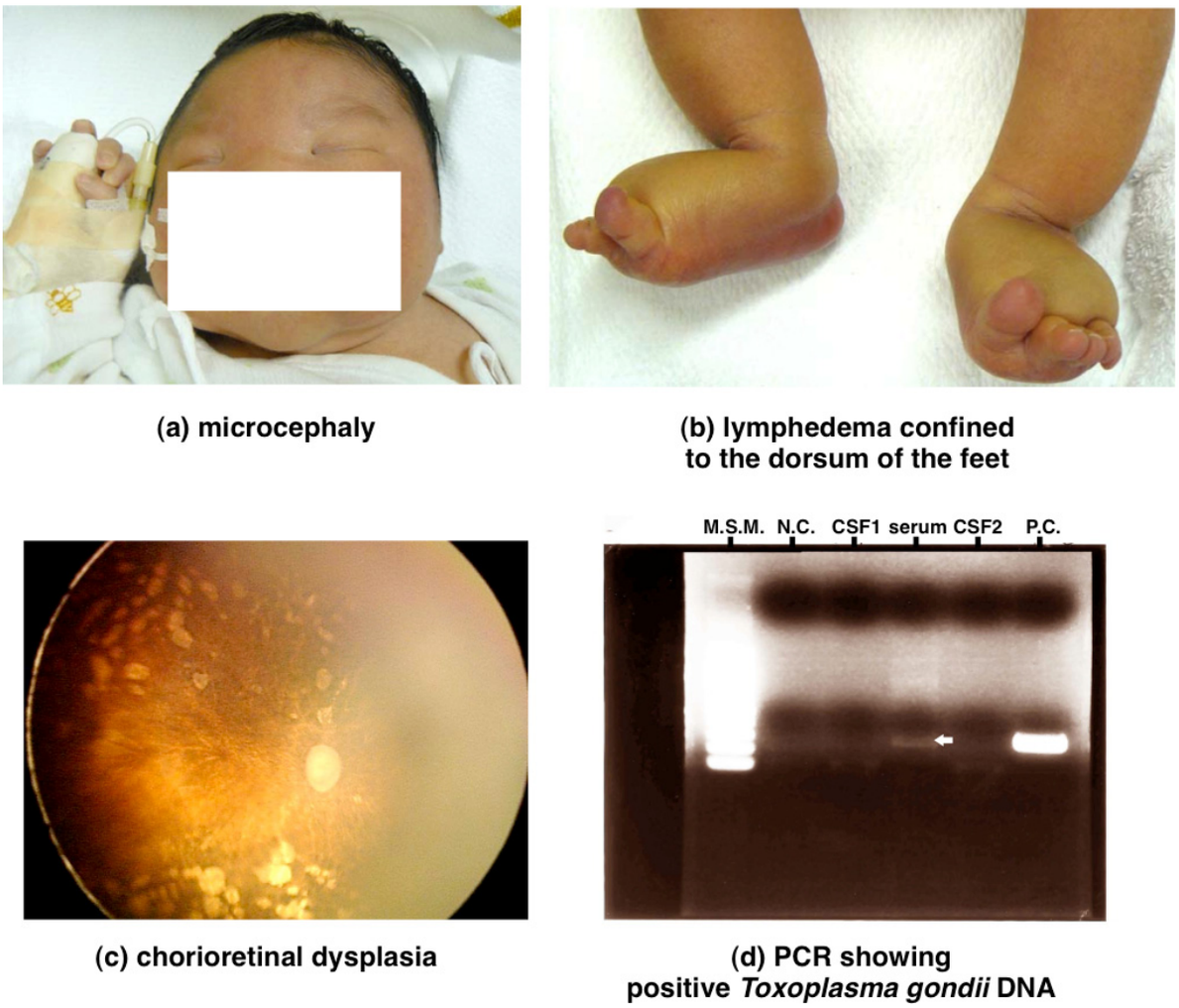

Figure 1.

3.3. Comment

The newborn presented with the complete triad of the MLCRD (2.4), i.e., microcephaly, lymphedema and chorioretinal dysplasia. (Table 1) He had apparent dorsal lymphedema that is hardly observed with toxoplasmosis. Brain calcifications, hydrocephalus, ascites or splenomegaly, that are more likely present in cases of congenital toxoplasmosis, could not be found. Moreover, *Toxoplasma* IgM was negative.

The present case indicates that suspected cases of congenital toxoplasmosis or pseudo toxoplasmosis should be examined for *Toxoplasma* DNA by PCR. (Ozeki et al., 2010)

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