A profile of childhood neuropathies at a University Hospital in Oman

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ABSTRACT

Objective: To analyze all cases of child childhood neuropathies (under 14 years of age) and report on their profile, pattern, clinical features and management.

Methods: Children with acute flaccid paralysis, longstanding weakness of extremities, neuroregression and children receiving anti cancer drugs with symptoms suggestive of neuropathy were evaluated for evidence of peripheral neuropathy. The evaluation of children with acute flaccid paralysis was a prospective study from January 1992 through to December 2000. The rest of the patients were studied retrospectively from the hospital medical records, pediatric neurology outpatient clinic and the neurophysiology laboratory, Sultan Qaboos University Hospital, Al-Khod, Oman

Results: Eighty-two (39 Male: 43 Female) children were found to have peripheral neuropathy. Acute Guillian-Barre syndrome was the most common with 37 children (45.1%), followed by genetic neuropathies [hereditary motor and sensory neuropathy with 17 (20.7%), hereditary sensory and autonomic neuropathy with 2 (2.4%), hereditary spastic paraplegia associated neuropathy with 9 (11%) and metachromatic leucodystrophy with 9 (11%)]. Chronic inflammatory demyelinating neuropathy was seen in 5 (6.1%) and vincristine induced neuropathy in 3 (3.5%) children.

Conclusion: Acute Guillian-Bare syndrome is the most common neuropathy amongst the acquired neuropathies. The treatable neuropathies constituted 54.7% (45 children) and the preventable genetic neuropathies accounted for the remaining 45.3% (37 children)

Keywords: Childhood neuropathies, Guillian-Barre syndrome, chronic inflammatory demyelinating neuropathy, hereditary neuropathies, metachromatic leucodystrophy, toxic neuropathy, prognosis.

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The childhood neuropathies are mainly constituted by hereditary neuropathies, neuropathies associated with metabolic and degenerative diseases of the nervous system. Seventy one percent of cases were found to be of genetic origin in one series and hereditary motor and sensory neuropathies were confirmed in over 40% of cases.[1] Modern immunohistochemical techniques and genetic studies combined with clinical and electrophysiologic work up, have brought radical changes in the classification and understanding of the pathophysiology of hereditary neuropathies.[2,3] These advances have made the use of certain invasive diagnostic procedures obsolete in the evaluation of disorders of the motor unit.[4] Amongst the acquired neuropathies, Guillian-Barre syndrome (GBS) and chronic inflammatory demyelinating neuropathy (CIDP) constitute nearly one 3rd of the neuropathies of childhood.[5] Neuropathies of childhood differ from the adult population. Hereditary neuropathies and GBS form the main group in childhood, while neuropathies of systemic disorders particularly diabetes mellitus

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constitute the largest group in adults. The present study was conducted at Sultan Qaboos University Hospital (SQUH) to ascertain the profile of childhood neuropathies in the Sultanate of Oman.

Methods. The study was carried out at SQUH, which is a tertiary care hospital for the country. All children under 14 years of age, confirmed to have neuropathy on electrophysiologic (nerve conduction) studies formed the subjects of the study. The study was prospective for acute GBS and CIDP, as part of an acute flaccid paralysis (AFP) surveillance, aimed at eradication of poliomyelitis from the Sultanate of Oman. The surveillance system and data collection began in January 1990.[6] Under this program, the Ministry of Health (MOH) implemented AFP surveillance at all levels of the national health care system involving all government hospitals, health facilities and private clinics. Training programs for AFP surveillance was provided to all health care personnel throughout the country, including physicians, nursing staff and paramedical workers. The patients included were from all over the country. All the AFP patients underwent blood examinations for immunoglobulin study, polio antibody titer and nerve conduction studies. At least 2 stool cultures for polio or other viruses were mandatory in all cases. The population of Oman is 1,483,226 of which 714,280 are aged under 15 years based on the census carried out from November 1992 through to January 1993.[7] Other children with neuropathies were picked up retrospectively from neurophysiology laboratory records, outpatient and inpatient records of our hospital. All children were admitted at one time or the other for detailed investigations. The diagnosis of different neuropathies was based on an internationally accepted, well-defined criteria. Acute GBS diagnosis was based on a criteria[8,9] defining it as an acute progressive symmetrical weakness of extremities with areflexia. The cerebro spinal fluid (CSF) showing albuminocytological disassociation and electrophysiology revealing features of demyelinating/axonal neuropathy. The diagnosis of CIDP was based on clinical features of acquired demyelinating neuropathy and progression of more than 2 months duration,[10] with nerve conduction studies showing features of demyelination with partial conduction block, temporal dispersion and focal slowing of multiple nerves. A nerve biopsy was carried out when the diagnosis was in doubt. The diagnosis of hereditary motor and sensory neuropathy (HMSN) was made in children with a family history of chronic neuropathy and features of uniform nerve conduction velocities on electrophysiologic sutdies.[11,12] Hereditary sensory and autonomic neuropathy (HSAN)[11] and hereditary spastic paraplegia (HSP) associated neuropathy[13,14] were diagnosed on well established clinical, electrophysiologic and laboratory data. The family history was of paramount importance in the case of genetic/hereditary neuropathies. The diagnosis of metachromatic leucodystrophy (MLD) neuropathy was made when neuropathy was detected in children with features of leukodystrophy. The diagnosis was confirmed on nerve biopsy. The facilities to assay arylsulphatase were not available in the beginning, however it was carried out in one child from an affected family when it became available. Trauma/ pressure related neuropathies, pressure palsies, plexus injuries, post injection neuritis for example, were not included in the study. All the patients included in the study are under follow up. Genetic studies are in progress in the various hereditary neuropathies.

Results. From January 1992 through to December 2000 (9 years), 82 cases of various neuropathies were diagnosed (**Table 1**). The important causes were GBS and hereditary neuropathies. There were 37 (20M: 17F) cases of GBS, males constituting 54%. Guillian-Barre syndrome was responsible for 45.1% cases of all neuropathies. Detailed clinical features of Guillain-Barre syndrome are outlined in **Table 2.** Bulbar palsies were noted in 5 (13.5%) children and 3rd and 6th nerve palsies in 3 each (8.1%). The autonomic nervous system was affected in 3 children (8.1%), hypertension in all and one in addition having tachycardia. The CSF examination was carried out at admission time, which meant, at least 2 days to one month after onset of GBS. The CSF cytology ranged form 0-60 cells/cmm, with one exception of 325cells/ cmm, the mean being 18 cells/cmm. The CSF

Table 1 - Pattern of childhood neuropathies.

All Cases					
S/N	**Type**	**Male**	**Female**	**Total**	**(%)**
1	GBS	20	17	**37**	45.1
2	CIDP	1	4	**5**	6.1
3	HMSN	8	9	**17**	20.7
4	HSAN	0	2	**2**	2.4
5	MLD	2	7	**9**	11
6	HSP	5	4	**9**	11
7	VCR	3	0	**3**	3.5
	Total	**39**	**43**	**82**	

GBS - guillain-barre syndrome
CIDP - chronic demyelinating inflammatory neuropathy
HMSN - hereditary motor and sensory neuropathy
HSAN - hereditary sensory and autonomic neuropathy
MLD - metachromatic leukodystrophy neuropathy
HSP - hereditary spastic paraplegia associated neuropathy
VCR - vincristine induced neuropathy
S/N - serial number

Table 2 - Detailed clinical features of Guillian-Barre syndrome.

Clinical Features	
N of cases	37 (20M:17F): 54% M: 46% F
Age group	1.5-11.5 years, mean: 4.6 years
Onset of weakness	1-30 days, mean: 8.9 days
Preceding events	22 children (59.5%)
URTI	18
Immunization OPV-2, MR-1	3
Meningeal signs	12 (32.4%)
Cranial nerves	22 (59.5%)
Facial nerves	18 (48.7%)
CSF cells/cmm	0-325, mean 18 cells
	Cells ≤ 5/cmm=22patients (59.5%)
Protein G/L	0.23-8, mean 1.83
IVIG	37 (one had plasmapheresis also)
Relapse	3 (8.1%)
Hospital stay in days	5-116, mean 20.4
Complete recovery in days	45-282, mean 73
Residual weakness	2 (5.4%)

N - number, M - male, F- female
URTI - upper respiratory tract infection
OPV - oral polio vaccine
MR - mumps rubella
CSF - cerebro spinal fluid
IVIG - intravenous immunoglobulin

proteins ranged from 0.23-8 G/L with a mean of 1.83 G/L. All patients were given intravenous immunoglobulins (IVIG), the dose being 400mg/kg/day for 5 days; one child underwent plasmapherisis. The recovery after IVIG was noted from 1-21 days after treatment with a mean of 5.8 days. Only 3 children out of 37 relapsed after receiving IVIG. Seven children had to be ventilated. The duration of hospital stay ranged from 5-116 days with a mean of 20.4 days. Out of a total of 37 cases, 25 (67.6%) patients were followed up until complete recovery at this hospital. The complete recovery was noted in 45-282 days with a mean of 73 days. The remaining 12 patients were referred back to peripheral hospitals after discharge. Only 2 children were left with residual weakness in the form of bilateral foot drop after 2 years of follow up. There was no mortality. Chronic demyelinating neuropathy was diagnosed in 5 children **(Table 3),** 4 of them being girls. The age of onset ranged from 5 to 9.5 years with a mean of 8.4 years. The CSF showed 5-7 lymphocytes/cmm with elevated proteins in all, ranging from 0.83 G/L to 1.8 G/L. All these children had at least more than 3 to 5 years follow up. All of them received 5 doses of IVIG (400mg/kg/dose), followed by methyl prednisolone (30mg/kg/dose x 3 doses). Oral prednisolone was administered to all patients for long periods and azathioprine was added when the response was poor. Two children have recovered completely with one still maintained on a small dose of prednisolone. The 3 others have shown frequent episodes of relapses and remissions. There was one child with peripheral nerve thickening (ulnar, greater auricular and common peroneals). This girl also had bilateral foot drop and pescavus. Nerve biopsy revealed lymphocytic infiltration and demyelination. Nerve conduction velocity (NCV) studies showed partial conduction blocks, temporal dispersions and focal slowing of velocities in multiple nerves. Even this patient showed significant recovery after one year of treatment.

There were 17 cases of HMSN and 2 cases of HSAN. The 17 cases of HMSN were from 7 families **(Table 4).** The age of onset varied from 1.9 years to 15 years, although the history of onset was vague in some cases. There was only one child with autosomal dominant type of HMSN manifesting as hypotonia and developmental delay at the age of 1.5 years, (the mother being the involved parent) and the rest were of autosomal recessive type. In one family, 5 children had the disease. Amongst the cases of HMSN, 8 were of demyelinating type and 9 of axonal/neuronal type. The 2 children with HSAN had ulcers on fingertips and soles**, (Figure 1)** with injury marks on the face and scalp. These girls were brought to the clinic at 1 year and 1.5 years of age. Metachromatic leucodystrophy neuropathy was diagnosed in 9 children from 3 families **(Table 5).** There were 4 children in one family, including a pair of twins. All the children had late infantile metachromatic leukodystrophy (MLD) and medical help was sought only after one year of age, with history of regression of milestones and difficulty in walking. Nerve conduction velocity studies were suggestive of demyelinating neuropathy in each of the index cases

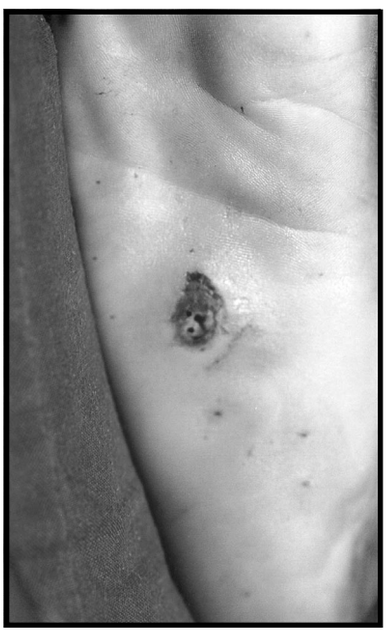

Figure 1 - Showing foot ulcer in a child with hereditary sensory and autonomic neuropathy.

Table 3 - Features of chronic inflammatory demyelinating neuropathy.

Features	
Total cases	5 (1M: 4F)
Age group	5-9.5 years, mean 8.4 years
CSF cells	5-7/ cmm
Protein	0.83-1.8 G/L
Treatment	IVIG + methyl prednisolone (prednisolone) + Azathioprine
Follow-up	3-6 years
Course	2 recovered, 3 frequent relapses & remissions

M - male, F - female
CSF - cerebrospinal fluid
IVIG - intravenous immunoglobulin

Table 5 - Features of metachromatic leukodystrophy neuropathy.

Features	
Total cases	9 (2M: 7F) 3 families (4 children in one family, including a pair of twins)
Type	Late infantile
CSF protein	Elevated (carried out in index cases)
Nerve conductions	Abnormal in all
Aryl sulphatase	Low (carried out only in one family)
Nerve biopsy	Confirmed (index case in each family)
CT brain scan	Abnormal in 4/9
MRI scan brain	Abnormal in 2/2

M - male, F - female
CSF cerebrospinal fluid
CT - computerized tomography
MRI - magentic resonance imaging

from the 3 families and were later confirmed by nerve biopsy **(Figure 2).** Aryl sulphatase assay carried out in one family index case was very low. Hereditary spastic paraplegia associated neuropathy was diagnosed in 9 cases (5M: 4F) from 4 families. There were 3 affected children in one family. Optic atrophy was seen only in one family with 2 affected children. Vincristine induced neuropathy was diagnosed in 3 children from the age group of 8-10 years **(Table 6).** All of them had acute lymphoblastic leukemia, and were in the induction phase of the treatment. The presenting features were difficulty in walking, paresthesia and food drop. By decreasing the dose of vincristine and increasing the dose interval there was considerable improvement and on follow up, for a period of more than 3 years, they were found to be asymptomatic clinically and electrophysiologically. The children recovered completely in approximately 8-12 weeks time.

Discussion. Peripheral neuropathies of childhood are predominantly constituted by hereditary neuropathies and neuropathies associated with metabolic and degenerative diseases of the central nervous system. Toxic neuropathies are extremely uncommon in children. In an overview of 125 biopsies proved subacute or chronic peripheral neuropathies occurring in children under 17 years of age, at least 71% of cases were considered to be genetic in origin.[1] Hereditary motor and sensory neuropathies were confirmed in over 40% of cases.[1] Amongst the adult population with peripheral

Table 4 - Details of hereditary motor and sensory neuropathy/hereditary sensory and autonomic neuropathy.

Features	
HMSN	
Total cases	17 (8M:9F) 7 families
Age of onset	1.9-15 years
Inheritance	
Autosomal dominant	1 (Mother affected)
Autosomal recessive	16
Type I	8 (4 families)
Type II	9 (3 families)
HSAN	
Total cases	2 girls (both autosomal recessive)
Age of onset	1 year and 1.5 years

HMSN - hereditary motor and sensory neuropathy
HSAN - hereditary sensory and autonomic neuropathy
M -male, F - female

Table 6 - Details of vincristine induced neuropathy.

Features	
VCR	
Total cases	3 (all boys)
Age group	8-10 years
Dose (post induction)	15mg/m^2
Clinical features	Gait abnormality + foot drop
Treatment	Dose reduced, interval prolonged
Follow up	3 years, symptom free

VCR - vincristine induced neuropathy

Figure 2 - Longitudinal section of nerve with metachromatic granules in Shwann cells (arrow) and endoneurial macrophages (frozen section-toluidine blue x 40).

neuropathy, chronic polyneuropathies of systemic disorders such as diabetes mellitus and toxic neuropathies constitute the largest group. However, GBS and CIDP constitute nearly one 3rd of immune mediated neuropathies of childhood.[5] The current nosological classification and terminology of the hereditary neuropathies of childhood are in a fluid state. Linkage of genes of these disorders to chromosomes one, 8, 17 and x and the finding of altered peripheral myelin protein have opened the gateway to better understanding of the pathophysiology of childhood neuropathies.[2,3] Alterations in the myotubularin related protein 2 (MTMP2) gene on chromosome 11qz have recently been shown to cause autosomal recessive demyelinating neuropathy in childhood.[15] These new diagnostic tools have changed the indications of certain invasive diagnostic procedures, in the evaluation of children with presumed disorders of the motor unit.[4]

Guillian-Barre syndrome (GBS). Guillian-Barre syndrome formed the major group of polyneuropathies (45.1%) in our current series, but accounted only for 20% of cases with AFP,[16] which, contrasts with another study where GBS formed 74% of total cases referred as AFP.[17] These GBS cases formed a part of AFP surveillance, an extremely sensitive monitoring system aimed at the global eradication of poliomyelitis, operational in many countries including the Sultanate of Oman, under the guidance of the World Health Organization (WHO). The present study is unique, as all the patients were hospitalized and followed up at Sultan Qaboos University Hospital, a national referral center. Thirty-seven cases of GBS were admitted over a period of 9 years from January 1992 through to December 2000 in the age group 1.5 years to 11.5 years, the mean age being 4.6 years. The annual incidence below 15 years in our study was 0.45/ 100,000. The age specific incidence was 1.26/ 100,000 in the age group 1-4 years and 0.24/100,000 in the 5-9 years age group.[16] No case was seen in the 10-15 years age group hence separate incidence was not calculated. A similar pattern has been well documented and is believed to be due to exposure of several infections, toxins and increased susceptibility of young myelin to demyelination.[17-19] Maximum weakness was observed at 1-30 days, the mean being 8.9 days. The facial nerve was the most common cranial nerve involved in GBS (18/22) followed by 10th, 3rd, and 6th cranial nerves. Cerebrospinal fluid analysis revealed that 22 of our patients (59.5%) had 5 or less lymphocytes/cmm. Cerebrospinal fluid proteins were elevated in 31 (83.8%), and normal in 2, while 4 patients refused lumbar puncture. Twenty (54.1%) children had a severe form of GBS and 7 children required ventilation from 7-46 days. One of them had to be reintubated and ventilated for 7 days, after relapse following use of IVIG. Two patients relapsed after 2 weeks of initial IVIG course. The earliest recovery sign (improvement by MRC scale grade 1) after IVIG, was documented after 24 hours of the first dose and the maximum time needed for onset of recovery was 21 days, with a mean of 5.8 days. By day 4 (4th dose of IVIG) 11 patients (30%) showed signs of recovery. Most of reports advocating the use of IVIG have documented dramatic improvement following this treatment,[20-22] though a few are not in favour.[23-25] Plasmapheresis was carried out only in one of our ventilated patients who also received IVIG. Some authors advocate that plasmapheresis is superior to IVIG in severe cases,[24] while many studies favor IVIG.[20,22] This was based on the fact that the group who underwent plasmapheresis had a higher relapse rate as compared to IVIG. Three patients (8.1%) showed initial improvement with IVIG and later relapsed within 2 weeks. One of these children had to be ventilated as repeat dose of IVIG did not prevent deterioration, while in the other 2 children repeat dose of IVIG helped in complete recovery. A very high relapse rate of 46.7% was reported with IVIG in one study,[25] while the Dutch study documented relapse rates as low as 1.4%.[22] Miller Fisher variant of GBS was seen in 3 and autonomic system was involved in another 3 children. The overall prognosis in children with GBS has been reported to be very good.[19,26] In our series only 2 (5.4%) children are left with minimal residual deficit, after 2 years of illness akin to a recently published study.[26]

Chronic inflammatory demyelinating neuropathy (CIDP). Chronic inflammatory demyelinating neuropathy is an acquired progressive neuropathy of more than 2 months duration with features of demyelination with partial conduction block, temporal dispersion and focal slowing of nerve conduction velocities (NCV) in multiple nerves.[10] Chronic inflammatory demyelinating neuropathy is rare in childhood, constituting 8.8% to 11.6% of

childhood neuropathies.[1,26,27] Five patients (6.1%) with CIDP were seen in our series. Out of these 5, one (20%) recovered completely and is off all medications, one (20%) is on the road to complete recovery on a small maintenance dose of prednisolone and the remaining 3 (60%) have been on relapsing courses. These 3 patients have been on combinations of azathiopine and prednisolone for the past 5 years. One of them is a chronic drug defaulter. In a review of 13 children with CIDP over a period of 15 years, it was found that there were 2 populations of children with CIDP.[28] The first subgroup has a favorable prognosis running a monophasic course with complete resolution of symptoms and signs, on withdrawal of medications, usually approximately one year after onset of illness. The 2nd subgroup requires prolonged medical treatment with considerable long-term morbidity and persistent weakness. Out of the 13 children with CIDP in the series mentioned above, it was noted that 3 children (23%) belonging to the first subgroup recovered completely while the remaining 10 (77.6%) had 1-4 relapses.[28] These 10 children (77.6%) had residual weakness after an average follow up of 6 years.

Hereditary neuropathies. The classifications of hereditary neuropathies have undergone drastic changes, since the original description by Dyck. The original classification of Dyck is based on the clinical, genetic and occasional biochemical characteristics. Recent advances in comprehending the molecular basis of these disorders has resulted in the modified version of Dyck's classification.[29] Our classification was based on clinical features and the hereditary pattern of these diseases, as facilities for molecular biology are not fully functional at the Sultan Qaboos University Hospital. Approximately 70% of chronic neuropathies seen in children are hereditary neuropathies.[1,29] In our study, hereditary neuropathies formed 45.1% of the total cases. If acute GBS is excluded, these chronic neuropathies would account for 82.2% of all cases in our series. Autosomal recessive form of HMSN was the most important hereditary neuropathy in our series, the type being demyelinating type 1 in 8 children and type 2 in 9 children. One child had autosomal dominant form of HMSN. Both the cases with HSAN were of type 2.

Hereditary spastic paraplegia (HSP) associated neuropathy. Hereditary spastic paraplegia associated neuropathy are of 2 types with pure and complicated.[14] The pure form is further divided into dominant, X-linked and recessive varieties. The pure form, characterized by spasticity rather than weakness and often associated with mild distal sensory loss, is seen in approximately 30% of affected families.[13] The complicated varieties have additional features and derive their names depending upon other sites of involvement in the nervous system, or their systemic manifestations. Nine children with HSP from 4 families were studied in our series, with one family having 3 affected children.

Metachromatic leukodystrophy (MLD). Metachromatic leukodystrophy neuropathy formed one of the important groups (11%) in our series. All the patients belonged to the subgroup of late infantile MLD. The diagnosis was confirmed in one index case of each family by nerve biopsy.[30] Amongst chemotherapeutic agents inducing neuropathy, vincristine was the drug involved.[29] These children recovered clinically completely in aproximately 8-12 weeks on reducing the dose of vincristine and increasing the interval of administration.

In conclusion, childhood neuropathies form an important neurological disorder in children. About 50% of cases are acquired and treatable, while, for the remaining half, new genetic tools are available to diagnose antenatally and possibly prevent them.

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